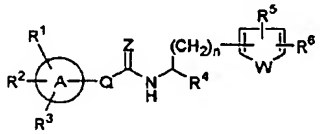
BQ1

Claim 1

A medicinal composition comprising containing a compound represented by formula (I) or pharmacologically acceptable salt thereof as effective component:



(I)

In the formula, ring A is aromatic hydrocarbon ring or heterocyclic,

Q is bond; carbonyl group; lower alkylene group which may be substituted by hydroxy group or phenyl group; lower alkenylene group; or -O-(lower alkylene)-group,

n is an integer of 0, 1 or 2,

W is oxygen atom, sulfur atom, -CH=CH- group or -N=CH- group,

Z is oxygen atom or sulfur atom,

R1, R2 and R3 may be the same or different and denote a group selected from the following groups,

a) a hydrogen atom,

b) a halogen atom,

c) a substituted- or unsubstituted-lower alkyl group,

d) a substituted- or unsubstituted-lower alkoxy group,

e) a nitro group,

f) a substituted- or unsubstituted-amino group,

g) a carboxyl group or ester or amide thereof,

h) a cyano group,

i) a lower alkyl thio group,

j) a lower alkane sulphonyl group,

k) a substituted- or unsubstituted-sulphamoyl group,

l) a substituted- or unsubstituted-aryl group,

m) a substituted- or unsubstituted-heterocyclic group and

n) hydroxy group, or two of R1, R2 and R3 may bond together at the terminals thereof and may form a lower alkylene dioxy group,

R4 is tetrazolyl group, carboxyl group, or amide or ester thereof

R5 is a group selected from the following groups

a) a hydrogen atom,

b) a nitro group,

c) a substituted- or unsubstituted-amino group,

d) a hydroxy group,

e) a lower alkanoyl group,

f) a substituted- or unsubstituted-lower alkyl group,

g) a lower alkoxy group,

h) a halogen atom and

i) 2-oxo pyrrolidinyl group,

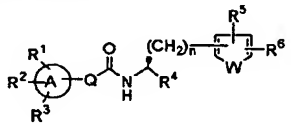
R6 is a group selected from the following groups

a) a substituted- or unsubstituted-phenyl group and

b) a substituted- or unsubstituted-heteroaryl group.

Claim 2

A medicinal composition in accordance with Claim 1, wherein the effective component is a compound represented by formula (I-A)

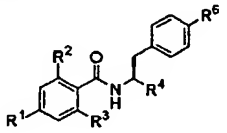


(I-A)

(wherein, each symbol is same as Claim 1).

Claim 3

A medicinal composition in accordance with Claim 1, wherein the effective component is a compound represented by formula (I-B)



(I-B)

(wherein, each symbol is same as Claim 1).

Claim 4

A medicinal composition in accordance with Claim 3, wherein R1 is hydrogen atom, halogen atom, carboxyl group, carbamoyl group, nitro group, substituted- or unsubstituted-amino group or substituted- or unsubstituted-heterocyclic group

R2 is hydrogen atom, lower alkyl group or halogen atom

R3 is hydrogen atom, lower alkyl group or halogen atom

R6 is phenyl group in which 2-position, 4-position and/or 6-position is optionally substituted by the group selected from the following groups

1) a halogen atom,

2) a substituted- or unsubstituted-lower alkoxy group,

3) a substituted- or unsubstituted-lower alkyl group,

4) a substituted- or unsubstituted-amino group,

5) a substituted- or unsubstituted-carbamoyl group and

6) a substituted- or unsubstituted-sulphamoyl group.

Claim 5

A medicinal composition in accordance with Claim 1, wherein ring A is benzene ring, pyridine ring, pyrazine ring, furan ring, isoxazole ring, benzofuran ring, thiophene ring, pyrrole ring or indole ring,

R1, R2 and R3 are the group selected from the following groups,

a) a hydrogen atom,

b) a halogen atom,

c) a lower alkyl group optionally substituted by halogen atom or halo benzoylamino group,

d) a lower alkoxy group optionally substituted by halogen atom,

e) a nitro group,

f) an amino group which may be substituted by one or two groups selected from 1) a lower alkyl group, 2) a lower alkanoyl group, 3) a halo benzoyl group, 4) a lower alkoxycarbonyl group, 5) a lower alkane sulphonyl group optionally substituted by halogen atom, 6) a benzenesulfonyl group optionally substituted by lower alkyl group, trihalo lower alkyl group, halogen atom or lower alkoxy group, 7) a thiophene sulphonyl group, 8) a carbamoyl group optionally substituted by lower alkyl group or lower alkyl phenyl group, 9) a thiocarbamoyl group optionally substituted by lower alkyl group, phenyl group or phenyl lower alkyl group, 10) a thiazolinyl group and 11) a sulphamoyl group optionally substituted by lower alkyl group,

g) a carboxyl group,

h) a carbamoyl group optionally substituted by lower alkane sulphonyl group,

i) a lower alkoxycarbonyl group,

j) a cyano group,

k) a lower alkyl thio group,

l) a lower alkane sulphonyl group,

m) a sulphamoyl group,

n) a phenyl group,

o) a pyrrolidinyl group optionally substituted by oxo group,

p) a pyrrolyl group optionally substituted by the group which is selected from 1) a lower alkanoyl group optionally substituted by a halogen atom, 2) a halogen atom, 3) a formyl group and 4) a lower alkyl group optionally substituted by hydroxy group,

q) a thienyl group,

r) an isoxazolyl group optionally substituted by lower alkyl group,

s) a thiazolyl group,

t) a pyrazolyl group,

u) a pyrazinyl group,

v) a pyridyl group and

w) a hydroxy group,

R4 is a group selected from the following groups,

a) a carboxyl group,

b) a lower alkoxycarbonyl group optionally substituted by 1) a pyridyl group or 2) an amino group optionally substituted by lower alkyl group,

c) a lower cycloalkoxycarbonyl group,

d) a carbamoyl group optionally substituted by hydroxy group or lower alkane sulphonyl group and

e) a tetrazolyl group,

R5 is a group selected from the following groups,

a) a hydrogen atom,

b) a nitro group,

c) an amino group optionally substituted by lower alkanoyl group, lower alkoxycarbonyl group or lower alkane sulphonyl group,

d) a hydroxy group,

e) a lower alkanoyl group,

f) a lower alkyl group optionally substituted by 1) a hydroxy group or 2) imino group substituted with hydroxy group or lower alkoxy group,

g) a lower alkoxy group,

h) a halogen atom and

i) a 2-oxo pyrrolidinyl group,

R6 is a group selected from the following groups,

a) a phenyl group optionally substituted by 1-5 groups selected from the following groups,

1) a halogen atom,

2) a nitro group,

3) a formyl group,

4) a hydroxy group,

5) a carboxyl group,

6) a lower alkoxy group optionally substituted by the group which is selected from i) a carboxyl group or an amide or ester thereof, ii) a hydroxy group, iii) a cyano group, iv) a halogen atom, v) an amino group optionally substituted by lower alkyl group, vi) a pyridyl group, vii) a thiazolyl group optionally substituted by lower alkyl group, viii) an isoxazolyl group optionally substituted by lower alkyl group, ix) a piperidyl group optionally substituted by lower alkyl group, x) a pyrrolidinyl group optionally substituted by lower alkyl group, xi) a phenyl group optionally substituted by halogen atom, xii) a furyl group, xiii) a thienyl group and xiv) a lower alkoxy group,

7) a lower alkyl group optionally substituted by a group selected from i) a halogen atom, ii) a hydroxy group, iii) a carboxyl group or an amide or ester thereof, iv) a lower alkoxy group, v) an amino group optionally substituted by 1-2 groups selected from the lower alkyl group, hydroxy lower alkyl group, lower alkyl amino lower alkyl group, phenyl lower alkyl group, phenyl group and pyridyl group, vi) a piperidinyl group optionally substituted by lower alkylene dihydroxy

group, oxo group or hydroxy group, vii) a morpholino group optionally substituted by lower alkyl group, viii) a thio morpholino group which may be oxidised, ix) a piperazinyl group optionally substituted by lower alkyl group, hydroxy lower alkyl group, lower alkanoyl group or phenyl lower alkyl group, x) a pyrrolidinyl group optionally substituted by oxo group and xi) an imidazolidinyl group optionally substituted by 1-3 groups selected from lower alkyl group and oxo group,

8) a lower alkenyl group optionally substituted by carboxyl group or amide or ester thereof,

9) an amino group optionally substituted by the group selected from i) a phenyl group, ii) a lower alkoxycarbonyl group, iii) a lower alkane sulphonyl group, iv) a carbamoyl group optionally substituted by lower alkyl group or lower alkyl phenyl group, v) a lower alkanoyl group, vi) a lower alkyl group, vii) a lower alkenyl group and viii) a thiocarbamoyl group optionally substituted by lower alkyl group,

10) a carbamoyl group optionally substituted by lower alkyl group, hydroxy lower alkyl group, morpholino lower alkyl group, phenyl lower alkyl group or lower alkane sulphonyl group,

11) a sulphamoyl group optionally substituted by the group selected from i) a lower alkyl group, ii) a benzoyl group, iii) a lower alkoxycarbonyl group and iv) a lower alkanoyl group,

12) a lower alkenyloxy group,

13) a lower alkylene dihydroxy group,

14) a piperazinyl carbonyl group optionally substituted by lower alkyl group,

15) a lower alkanoyl group,

16) a cyano group,

17) a lower alkyl thio group,

18) a lower alkane sulphonyl group,

19) a lower alkyl sulfinyl group and

20) a group represented by formula –(CH2)q-O- (wherein, q is an integer of 2 or 3),

b) a pyridyl group optionally substituted by lower alkyl group,

c) a thienyl group optionally substituted by the group selected from the following groups,

1) a halogen atom,

2) a lower alkyl group optionally substituted by hydroxy group,

3) a cyano group,

4) a formyl group,

5) a lower alkoxy group and

6) a lower alkanoyl group,

d) a benzofuranyl group,

e) a pyrimidinyl group optionally substituted by lower alkoxy group,

f) an isoxazolyl group optionally substituted by lower alkyl group and

g) a pyrrolyl group optionally substituted by lower alkoxycarbonyl group.

Claim 6

A medicinal composition in accordance with Claim 5, wherein ring A is benzene ring, Q is a bond, W is -CH=CH-, R1 is a group selected from the following groups,

a) a hydrogen atom,

b) a halogen atom,

c) a lower alkyl group,

d) a lower alkoxy group,

e) a nitro group,

f) an amino group optionally substituted by a group selected from 1) a lower alkyl group, 2) a lower alkanoyl group, 3) a lower alkoxycarbonyl group, 4) a lower alkane sulphonyl group optionally substituted by halogen atom, 5) a benzenesulfonyl group optionally substituted by lower alkyl group, trihalo lower alkyl group, halogen atom or lower alkoxy group, 6) a thiophene sulphonyl group, 7) a carbamoyl group optionally substituted by lower alkyl group or lower alkyl phenyl group, 8) a thiocarbamoyl group optionally substituted by lower alkyl group and 9) a sulphamoyl group optionally substituted by lower alkyl group,

g) a carboxyl group,

h) a carbamoyl group optionally substituted by lower alkane sulphonyl group,

i) a lower alkane sulphonyl group,

j) a sulphamoyl group,

k) a phenyl group,

l) a pyrrolidinyl group optionally substituted by oxo group,

l) a pyrrolyl group optionally substituted by lower alkyl group,

m) a thienyl group,

n) an isoxazolyl group optionally substituted by lower alkyl group,

o) a thiazolyl group,

p) a pyrazolyl group,

q) a pyrazinyl group,

r) a pyridyl group and

s) a hydroxy group,

R2 is a hydrogen atom or halogen atom, R3 is a hydrogen atom or halogen atom, R4 is a) a carboxyl group, b) a lower alkoxycarbonyl group optionally substituted by lower alkyl amino group or c) a carbamoyl group optionally substituted by a lower alkane sulphonyl group, R5 is a group selected from the following groups,

a) a hydrogen atom,

b) an amino group optionally substituted by lower alkanoyl group, lower alkoxycarbonyl group or lower alkane sulphonyl group,

c) a lower alkanoyl group,

d) a lower alkyl group optionally substituted by 1) a hydroxy group or 2) imino group substituted by hydroxy group or lower alkoxy group,

e) a lower alkoxy group and

f) a halogen atom,

R6 is a phenyl group optionally substituted by 1-5 groups selected from the following groups

a) a halogen atom,

b) a formyl group,

c) a hydroxy group,

d) a lower alkoxy group optionally substituted by 1) a carboxyl group, 2) a hydroxy group, 3) a cyano group, 4) a halogen atom, 5) an amino group optionally substituted by lower alkyl group, 6) a pyridyl group, 7) a phenyl group, 8) a thienyl group or 9) a lower alkoxy group,

e) a lower alkyl group optionally substituted by 1) an amino group optionally substituted by lower alkyl group, hydroxy lower alkyl group, lower alkyl amino lower alkyl group or phenyl group, 2) a piperidinyl group optionally substituted by lower alkylene dihydroxy group, 3) a morpholino group optionally substituted by lower alkyl group, 4) a thio morpholino group in which sulfur atom may be oxidised, 5) a piperazinyl group optionally substituted by lower alkyl group, hydroxy lower alkyl group, lower alkanoyl group or phenyl lower alkyl group, 6) a pyrrolidinyl group optionally substituted by oxo group or 7) an imidazolidinyl group optionally substituted by 1-3 groups selected from the oxo group and lower alkyl group,

f) an amino group optionally substituted by 1) a lower alkoxycarbonyl group, 2) a lower alkane sulphonyl group, 3) a carbamoyl group optionally substituted by lower alkyl group or lower alkyl phenyl group, 4) a lower alkanoyl group, 5) a lower alkyl group, 6) a lower alkenyl group or 7) a thiocarbamoyl group optionally substituted by lower alkyl group,

g) a carbamoyl group optionally substituted by 1) a lower alkyl group, 2) a hydroxy lower alkyl group, 3) a morpholino lower alkyl group, 4) a phenyl lower alkyl group or 5) a lower alkane sulphonyl group,

h) a sulphamoyl group optionally substituted by lower alkyl group,

i) a lower alkenyloxy group,

j) a lower alkylene dihydroxy group,

k) a cyano group,

l) a lower alkyl thio group and

m) a lower alkane sulphonyl group.

Claim 7

A medicinal composition in accordance with any of Claim 4, 5, 6, wherein

R1 is 1) a hydrogen atom, 2) a halogen atom, 3) a lower alkanoyl amino group, 4) a lower alkoxycarbonylamino group, 5) a lower alkane sulfonyl amino group optionally substituted by halogen atom, 6) a benzensulphonyl amino group optionally substituted by lower alkyl group,

trihalo lower alkyl group, halogen atom or lower alkoxy group, 7) a thiophene sulfonyl amino group, 8) an ureide group optionally substituted by lower alkyl group or lower alkyl phenyl group, 9) a lower alkyl thiouredide group or 10) a lower alkyl sulphamoyl amino group,

R2 is a halogen atom,

R3 is a hydrogen atom or halogen atom,

R6 is a phenyl group optionally substituted by 1-3 groups selected from 1) a lower alkoxy group, 2) a lower alkyl group optionally substituted by 1-3 groups selected from the lower alkyl amino group, hydroxy lower alkyl amino group, lower alkyl amino lower alkyl amino group, piperidinyl group, lower alkyl piperidinyl group, morpholino group, lower alkyl morpholino group, thio morpholino group, piperazinyl group, lower alkyl piperazinyl group, lower alkanoyl piperazinyl group and pyrrolidinyl group, 3) a sulphamoyl group optionally substituted by lower alkyl group and 4) a carbamoyl group optionally substituted by lower alkyl group.

Claim 8

A medicinal composition in accordance with Claim 7, wherein R1 is a hydrogen atom, R3 is a halogen atom and R6 is 2-lower alkyloxyphenyl group, 2,6-dilower alkyloxyphenyl group, 2,6-dilower alkoxy-4-[[N,N-dilower alkyl amino] lower alkyl] phenyl group, 2,6-dilower alkoxy-4-[(4-lower alkyl-1-piperazinyl) lower alkyl] phenyl group, 2,6-dilower alkoxy-4-[1-piperidinyl lower alkyl] phenyl group, 2,6-dilower alkoxy-4-[N,N-di (lower alkyl) carbamoyl] phenyl group or 2,6-dilower alkoxy-4-[(morpholino) lower alkyl] phenyl group.

Claim 9

A medicinal composition in accordance with Claim 8, wherein the lower alkoxy is methoxy.

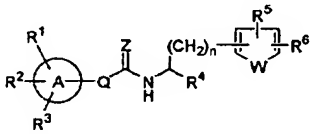
Claim 10

A medicinal composition containing following compound, lower alkyl ester thereof or pharmacologically acceptable salt thereof as effective component: N-(2,6-dichlorobenzoyl)-4-(2,6-dimethoxyphenyl)-L-phenylalanine, N-(2,6-dichlorobenzoyl)-4-[2,6-dimethoxy-4-(1-piperidinomethyl) phenyl]-L-phenylalanine, N-(2,6-dichlorobenzoyl)-4-[2,6-dimethoxy-4-[(4-methyl piperazinyl) methyl] phenyl]-L-phenylalanine, N-(2,6-dichlorobenzoyl)-4-[2,6-dimethoxy-4-(morpholinomethyl) phenyl]-L-phenylalanine, N-(2,6-dichlorobenzoyl)-4-[2,6-dimethoxy-4-[(N,N-dimethylamino) methyl] phenyl]-L-phenylalanine, N-(2,6-dichlorobenzoyl)-4-[2,6-dimethoxy-4-(N,N-dimethylcarbamoyl) phenyl]-L-phenylalanine, N-(2,6-dichloro-4-hydroxybenzoyl)-4-(2,6-dimethoxyphenyl)-L-phenylalanine, N-(2,6-dichlorobenzoyl)-4-(2-ethoxy-6-methoxyphenyl)-L-phenylalanine, N-(2,6-difluorobenzoyl)-4-(2,6-dimethoxyphenyl)-L-phenylalanine, N-(2,6-dichlorobenzoyl)-4-(2,3-methylenedioxy-6-methoxyphenyl)-L-phenylalanine, N-(2,6-dichlorobenzoyl)-3-(1-hydroxyethyl)-4-(2,6-dimethoxyphenyl)-L-phenylalanine, N-(2,6-dichlorobenzoyl)-4-(2,4,6-trimethoxyphenyl)-L-phenylalanine, N-[2,6-

dichloro-4-[(trifluoromethane sulfonyl) amino] benzoyl]-4-(2,6-dimethoxyphenyl)-L-phenylalanine or N-[2,6-dichloro-4-[(2-thienylsulfonyl) amino] benzoyl]-4-(2,6-dimethoxyphenyl)-L-phenylalanine.

Claim 11

A medicinal composition for therapy or prevent for the pathological state due to alpha 4-mediated cell adhesion comprising containing as effective component, a compound represented by formula (I) or a pharmacologically acceptable salt thereof



(I)

In the formula, ring A is aromatic hydrocarbon ring or heterocyclic,

Q is bond; carbonyl group; lower alkylene group which may be substituted by hydroxy group or phenyl group; lower alkenylene group; or -O-(lower alkylene)-group,

n is an integer of 0, 1 or 2,

W is oxygen atom, sulfur atom, -CH=CH- group or -N=CH- group,

Z is oxygen atom or sulfur atom,

R1, R2 and R3 may be the same or different and denote a group selected from the following groups,

a) a hydrogen atom,

b) a halogen atom,

c) a substituted- or unsubstituted-lower alkyl group,

d) a substituted- or unsubstituted-lower alkoxy group,

e) a nitro group,

f) a substituted- or unsubstituted-amino group,

g) a carboxyl group or ester or amide thereof,

h) a cyano group,

i) a lower alkyl thio group,

j) a lower alkane sulphonyl group,

k) a substituted- or unsubstituted-sulphamoyl group,

l) a substituted- or unsubstituted-aryl group,

m) a substituted- or unsubstituted-heterocyclic group and

n) hydroxy group, or two groups of R1, R2 and R3 bond together on terminal thereof and may form lower alkylene dihydroxy group,

R4 is tetrazolyl group, carboxyl group, or amide or ester thereof

R5 is a group selected from the following groups

a) a hydrogen atom,

b) a nitro group,

c) a substituted- or unsubstituted-amino group,

d) a hydroxy group,

e) a lower alkanoyl group,

f) a substituted- or unsubstituted-lower alkyl group,

g) a lower alkoxy group,

h) a halogen atom and

i) 2-oxo pyrrolidinyl group,

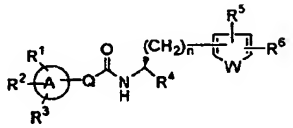
R6 is a group selected from the following groups

a) a substituted- or unsubstituted-phenyl group and

b) a substituted- or unsubstituted-heteroaryl group.

Claim 12

A medicinal composition in accordance with Claim 11, wherein the effective component is a compound represented by formula (I-A)

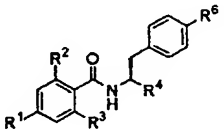


(I-A)

(wherein, each symbol has the same meaning as in Claim 11).

Claim 13

A medicinal composition in accordance with Claim 12, wherein the effective component is a compound represented by formula (I-B)



(I-B)

(wherein, each symbol has the same meaning as in Claim 11).

Claim 14

A medicinal composition in accordance with Claim 13, wherein

R1 is hydrogen atom, halogen atom, carboxyl group, carbamoyl group, nitro group, substituted- or unsubstituted-amino group or substituted- or unsubstituted-heterocyclic group,

R2 is a hydrogen atom, lower alkyl group or halogen atom,

R3 is a hydrogen atom, lower alkyl group or halogen atom and

R6 is phenyl group in which 2 position, 4 position and/or 6 position is optionally substituted by the group selected from the following groups

1) a halogen atom,

2) a substituted- or unsubstituted-lower alkoxy group,

3) a substituted- or unsubstituted-lower alkyl group,

4) a substituted- or unsubstituted-amino group,

5) a substituted- or unsubstituted-carbamoyl group and

6) a substituted- or unsubstituted-sulphamoyl group.

Claim 15

A medicinal composition in accordance with Claim 11, wherein ring A is benzene ring, pyridine ring, pyrazine ring, furan ring, isoxazole ring, benzofuran ring, thiophene ring, pyrrole ring or indole ring,

R1, R2 and R3 are the groups selected from the following groups,

a) a hydrogen atom,

b) a halogen atom,

c) a lower alkyl group optionally substituted by halogen atom or halo benzoylamino group,

d) a lower alkoxy group optionally substituted by halogen atom,

e) a nitro group,

f) an amino group which may be substituted by one or two groups selected from 1) a lower alkyl group, 2) a lower alkanoyl group, 3) a halo benzoyl group, 4) a lower alkoxycarbonyl group, 5) a lower alkane sulphonyl group optionally substituted by halogen atom, 6) a benzenesulfonyl group optionally substituted by lower alkyl group, trihalo lower alkyl group, halogen atom or lower alkoxy group, 7) a thiophene sulphonyl group, 8) a carbamoyl group optionally substituted by lower alkyl group or lower alkyl phenyl group, 9) a thiocarbamoyl group optionally substituted by lower alkyl group, phenyl group or phenyl lower alkyl group, 10) a thiazolinyl group and 11) a sulphamoyl group optionally substituted by lower alkyl group,

g) a carboxyl group,

h) a carbamoyl group optionally substituted by lower alkane sulphonyl group,

i) a lower alkoxycarbonyl group,

j) a cyano group,

k) a lower alkyl thio group,

l) a lower alkane sulphonyl group,

m) a sulphamoyl group,

n) a phenyl group,

o) a pyrrolidinyl group optionally substituted by oxo group,

p) a pyrrolyl group optionally substituted by the group which is selected from 1) a lower alkanoyl group optionally substituted by a halogen atom, 2) a halogen atom, 3) a formyl group and 4) a lower alkyl group optionally substituted by hydroxy group,

q) a thienyl group,

r) an isoxazolyl group optionally substituted by lower alkyl group,

s) a thiazolyl group,

t) a pyrazolyl group,

u) a pyrazinyl group,

v) a pyridyl group and

w) a hydroxy group,

R4 is a group selected from the following groups,

a) a carboxyl group,

b) a lower alkoxycarbonyl group optionally substituted by 1) a pyridyl group or 2) an amino group optionally substituted by lower alkyl group,

c) a lower cycloalkoxycarbonyl group,

d) a carbamoyl group optionally substituted by hydroxy group or lower alkane sulphonyl group and

e) a tetrazolyl group,

R5 is a group selected from the following groups,

a) a hydrogen atom,

b) a nitro group,

c) an amino group optionally substituted by lower alkanoyl group, lower alkoxycarbonyl group or lower alkane sulphonyl group,

d) a hydroxy group,

e) a lower alkanoyl group,

f) a lower alkyl group optionally substituted by 1) a hydroxy group or 2) imino group substituted with hydroxy group or lower alkoxy group,

g) a lower alkoxy group,

h) a halogen atom and

i) a 2-oxo pyrrolidinyl group,

R6 is a group selected from the following groups,

a) a phenyl group optionally substituted by 1-5 groups selected from the following groups,

1) a halogen atom,

2) a nitro group,

3) a formyl group,

4) a hydroxy group,

5) a carboxyl group,

6) a lower alkoxy group optionally substituted by the group which is selected from i) a carboxyl group or an amide or ester thereof, ii) a hydroxy group, iii) a cyano group, iv) a halogen atom, v) an amino group optionally substituted by lower alkyl group, vi) a pyridyl group, vii) a thiazolyl group optionally substituted by lower alkyl group, viii) an isoxazolyl group optionally substituted by lower alkyl group, ix) a piperidyl group optionally substituted by lower alkyl group, x) a pyrrolidinyl group optionally substituted by lower alkyl group, xi) a phenyl group optionally substituted by halogen atom, xii) a furyl group, xiii) a thienyl group and xiv) a lower alkoxy group,

7) a lower alkyl group optionally substituted by a group selected from i) a halogen atom, ii) a hydroxy group, iii) a carboxyl group or an amide or ester thereof, iv) a lower alkoxy group, v) an amino group optionally substituted by 1-2 groups selected from the lower alkyl group, hydroxy lower alkyl group, lower alkyl amino lower alkyl group, phenyl lower alkyl group, phenyl group and pyridyl group, vi) a piperidinyl group optionally substituted by lower alkylene dihydroxy group, oxo group or hydroxy group, vii) a morpholino group optionally substituted by lower alkyl group, viii) a thio morpholino group which may be oxidised, ix) a piperazinyl group optionally substituted by lower alkyl group, hydroxy lower alkyl group, lower alkanoyl group or phenyl lower alkyl group, x) a pyrrolidinyl group optionally substituted by oxo group and xi) an imidazolidinyl group optionally substituted by 1-3 groups selected from lower alkyl group and oxo group,

8) a lower alkenyl group optionally substituted by carboxyl group or amide or ester thereof,

9) an amino group optionally substituted by the group selected from i) a phenyl group, ii) a lower alkoxycarbonyl group, iii) a lower alkane sulphonyl group, iv) a carbamoyl group optionally substituted by lower alkyl group or lower alkyl phenyl group, v) a lower alkanoyl group, vi) a lower alkyl group, vii) a lower alkenyl group and viii) a thiocarbamoyl group optionally substituted by lower alkyl group,

10) a carbamoyl group optionally substituted by lower alkyl group, hydroxy lower alkyl group, morpholino lower alkyl group, phenyl lower alkyl group or lower alkane sulphonyl group,

11) a sulphamoyl group optionally substituted by the group selected from i) a lower alkyl group, ii) a benzoyl group, iii) a lower alkoxycarbonyl group and iv) a lower alkanoyl group,

12) a lower alkenyloxy group,

13) a lower alkylene dihydroxy group,

14) a piperazinyl carbonyl group optionally substituted by lower alkyl group,

15) a lower alkanoyl group,

16) a cyano group,

17) a lower alkyl thio group,

18) a lower alkane sulphonyl group,

19) a lower alkyl sulfinyl group and

20) a group represented by formula –(CH2)q-O- (wherein, q is an integer of 2 or 3),

b) a pyridyl group optionally substituted by lower alkyl group,

c) a thienyl group optionally substituted by the group selected from the following groups,

1) a halogen atom,

2) a lower alkyl group optionally substituted by hydroxy group,

3) a cyano group,

4) a formyl group,

5) a lower alkoxy group and

6) a lower alkanoyl group,

d) a benzofuranyl group,

e) a pyrimidinyl group optionally substituted by lower alkoxy group,

f) an isoxazolyl group optionally substituted by lower alkyl group and

g) a pyrrolyl group optionally substituted by lower alkoxycarbonyl group.

Claim 16

A medicinal composition in accordance with Claim 15, wherein ring A is benzene ring, Q is a bond, W is -CH=CH-, R1 is a group selected from the following groups,

a) a hydrogen atom,

b) a halogen atom,

c) a lower alkyl group,

d) a lower alkoxy group,

e) a nitro group,

f) an amino group optionally substituted by a group selected from 1) a lower alkyl group, 2) a lower alkanoyl group, 3) a lower alkoxycarbonyl group, 4) a lower alkane sulphonyl group optionally substituted by halogen atom, 5) a benzenesulfonyl group optionally substituted by lower alkyl group, trihalo lower alkyl group, halogen atom or lower alkoxy group, 6) a thiophene sulphonyl group, 7) a carbamoyl group optionally substituted by lower alkyl group or lower alkyl phenyl group, 8) a thiocarbamoyl group optionally substituted by lower alkyl group and 9) a sulphamoyl group optionally substituted by lower alkyl group,

g) a carboxyl group,

h) a carbamoyl group optionally substituted by lower alkane sulphonyl group,

i) a lower alkane sulphonyl group,

j) a sulphamoyl group,

k) a phenyl group,

l) a pyrrolidinyl group optionally substituted by oxo group,

l) a pyrrolyl group optionally substituted by lower alkyl group,

m) a thienyl group,

n) an isoxazolyl group optionally substituted by lower alkyl group,

o) a thiazolyl group,

p) a pyrazolyl group,

q) a pyrazinyl group,

r) a pyridyl group and

s) a hydroxy group,

R2 is a hydrogen atom or halogen atom, R3 is a hydrogen atom or halogen atom, R4 is a) a carboxyl group, b) a lower alkoxycarbonyl group optionally substituted by lower alkyl amino group or c) a carbamoyl group optionally substituted by lower alkane sulphonyl group, R5 is a group selected from the following groups,

a) a hydrogen atom,

b) an amino group optionally substituted by lower alkanoyl group, lower alkoxycarbonyl group or lower alkane sulphonyl group,

c) a lower alkanoyl group,

d) a lower alkyl group optionally substituted by 1) a hydroxy group or 2) imino group substituted by hydroxy group or lower alkoxy group,

e) a lower alkoxy group and

f) a halogen atom,

R6 is a phenyl group optionally substituted by 1-5 groups selected from the following groups

a) a halogen atom,

b) a formyl group,

c) a hydroxy group,

d) a lower alkoxy group optionally substituted by 1) a carboxyl group, 2) a hydroxy group, 3) a cyano group, 4) a halogen atom, 5) an amino group optionally substituted by lower alkyl group, 6) a pyridyl group, 7) a phenyl group, 8) a thienyl group or 9) a lower alkoxy group,

e) a lower alkyl group optionally substituted by 1) an amino group optionally substituted by lower alkyl group, hydroxy lower alkyl group, lower alkyl amino lower alkyl group or phenyl group, 2) a piperidinyl group optionally substituted by lower alkylene dihydroxy group, 3) a morpholino group optionally substituted by lower alkyl group, 4) a thio morpholino group in which sulfur atom may be oxidised, 5) a piperazinyl group optionally substituted by lower alkyl group, hydroxy lower alkyl group, lower alkanoyl group or phenyl lower alkyl group, 6) a pyrrolidinyl group optionally substituted by oxo group or 7) an imidazolidinyl group optionally substituted by 1-3 groups selected from the oxo group and lower alkyl group,

f) an amino group optionally substituted by 1) a lower alkoxycarbonyl group, 2) a lower alkane sulphonyl group, 3) a carbamoyl group optionally substituted by lower alkyl group or lower alkyl phenyl group, 4) a lower alkanoyl group, 5) a lower alkyl group, 6) a lower alkenyl group or 7) a thiocarbamoyl group optionally substituted by lower alkyl group,

g) a carbamoyl group optionally substituted by 1) a lower alkyl group, 2) a hydroxy lower alkyl group, 3) a morpholino lower alkyl group, 4) a phenyl lower alkyl group or 5) a lower alkane sulphonyl group,

h) a sulphamoyl group optionally substituted by lower alkyl group,

i) a lower alkenyloxy group,

j) a lower alkylene dihydroxy group,

k) a cyano group,

l) a lower alkyl thio group and

m) a lower alkane sulphonyl group.

Claim 17

A medicinal composition in accordance with any of Claim 14, 15, 16, wherein

R1 is 1) a hydrogen atom, 2) a halogen atom, 3) a lower alkanoyl amino group, 4) a lower alkoxycarbonylamino group, 5) a lower alkane sulfonyl amino group optionally substituted by halogen atom, 6) a benzensulphonyl amino group optionally substituted by lower alkyl group, trihalo lower alkyl group, halogen atom or lower alkoxy group, 7) a thiophene sulfonyl amino group, 8) an ureide group optionally substituted by lower alkyl group or lower alkyl phenyl group, 9) a lower alkyl thiouredide group or 10) a lower alkyl sulphamoyl amino group,

R2 is a halogen atom,

R3 is a hydrogen atom or halogen atom,

R6 is a phenyl group optionally substituted by 1-3 groups selected from 1) a lower alkoxy group, 2) a lower alkyl group optionally substituted by 1-3 groups selected from the lower alkyl amino group, hydroxy lower alkyl amino group, lower alkyl amino lower alkyl amino group, piperidinyl group, lower alkyl piperidinyl group, morpholino group, lower alkyl morpholino group, thio morpholino group, piperazinyl group, lower alkyl piperazinyl group, lower alkanoyl piperazinyl group and pyrrolidinyl group, 3) a sulphamoyl group optionally substituted by lower alkyl group and 4) a carbamoyl group optionally substituted by lower alkyl group.

Claim 18

A medicinal composition in accordance with Claim 17, wherein R1 is a hydrogen atom, R3 is a halogen atom and R6 is 2-lower alkyloxyphenyl group, 2,6-dilower alkyloxyphenyl group, 2,6-dilower alkoxy-4-[[N,N-dilower alkyl amino] lower alkyl] phenyl group, 2,6-dilower alkoxy-4-[(4-lower alkyl-1-piperazinyl) lower alkyl] phenyl group, 2,6-dilower alkoxy-4-[1-piperidinyl lower alkyl] phenyl group, 2,6-dilower alkoxy-4-[N,N-di (lower alkyl) carbamoyl] phenyl group or 2,6-dilower alkoxy-4-[(morpholino) lower alkyl] phenyl group.

Claim 19

A medicinal composition in accordance with Claim 18, wherein the lower alkoxy is methoxy.

Claim 20

A medicinal composition for therapy or prevent for the pathological state due to alpha 4-mediated cell adhesion comprising containing as effective component, following compound, lower alkyl ester thereof or pharmacologically acceptable salt thereof. N-(2,6-dichlorobenzoyl)-4-(2,6-dimethoxyphenyl)-L-phenylalanine, N-(2,6-dichlorobenzoyl)-4-[2,6-dimethoxy-4-(1-piperidinomethyl) phenyl]-L-phenylalanine, N-(2,6-dichlorobenzoyl)-4-[2,6-dimethoxy-4-[(4-methyl piperazinyl) methyl] phenyl]-L-phenylalanine, N-(2,6-dichlorobenzoyl)-4-[2,6-dimethoxy-4-(morpholinomethyl) phenyl]-L-phenylalanine, N-(2,6-dichlorobenzoyl)-4-[2,6-dimethoxy-4-[(N,N-dimethylamino) methyl] phenyl]-L-phenylalanine, N-(2,6-dichlorobenzoyl)-4-[2,6-dimethoxy-4-(N,N-dimethylcarbamoyl) phenyl]-L-phenylalanine, N-(2,6-dichloro-4-

hydroxybenzoyl)-4-(2,6-dimethoxyphenyl)-L-phenylalanine, N-(2,6-dichlorobenzoyl)-4-(2-ethoxy-6-methoxyphenyl)-L-phenylalanine, N-(2,6-difluorobenzoyl)-4-(2,6-dimethoxyphenyl)-L-phenylalanine, N-(2,6-dichlorobenzoyl)-4-(2,3-methylene dioxy-6-methoxyphenyl)-L-phenylalanine, N-(2,6-dichlorobenzoyl)-3-(1-hydroxyethyl)-4-(2,6-dimethoxyphenyl)-L-phenylalanine, N-(2,6-dichlorobenzoyl)-4-(2,4,6-trimethoxyphenyl)-L-phenylalanine, N-[2,6-dichloro-4-[(trifluoromethane sulfonyl) amino] benzoyl]-4-(2,6-dimethoxyphenyl)-L-phenylalanine or N-[2,6-dichloro-4-[(2-thienylsulfonyl) amino] benzoyl]-4-(2,6-dimethoxyphenyl)-L-phenylalanine.

Claim 21

A medicinal composition in accordance with any one of Claims 11-20, wherein the pathological state due to alpha 4-mediated cell adhesion is a pathological state accompanied with leukocyte infiltration in tissue.

Claim 22

A medicinal composition in accordance with Claim 21, wherein the pathological state accompanied with leukocyte infiltration in tissue is a pathological state accompanied with leukocyte infiltration in epithelial tissue, lung, blood vessel, heart, nerve tissue, transplanted organ.

Claim 23

A medicinal composition in accordance with Claim 22, wherein the pathological state accompanied with leukocyte infiltration in epithelial tissue is a pathological state accompanied with leukocyte infiltration in gastrointestinal tract, skin, urethra, trachea or articulation synovial membrane.

Claim 24

A medicinal composition in accordance with Claim 22, wherein the pathological state accompanied with leukocyte infiltration in transplanted organ is a pathological state accompanied with leukocyte infiltration in transplanted kidney, liver, pancreas or heart.

Claim 25

A medicinal composition in accordance with Claim 21, wherein the pathological state accompanied with leukocyte infiltration in tissue is arthritis rheumatica, asthma, psoriasis, dermatitis disease, diabetes mellitus, multiple sclerosis, systemic erythematodes (SLE), inflammatory enteric disease or graft versus host disease.

Claim 26

A medicinal composition in accordance with Claim 25, wherein the dermatitis disease is eczema, contact dermatitis or atopic dermatitis, and inflammatory enteric disease is ulcerative colitis or Crohn's disease.

Detailed Description.

Detailed Description of the Invention

(0001)

Technical Sphere of the Invention

This invention relates to the following, namely a medicinal composition, containing as an active ingredient, α4-mediated adhesion inhibitor including α4β7, which is effective in therapy of pathological state such as asthma, diabetes mellitus, rheumatism arthritis and inflammatory enteric disease, and in addition to these the disease or the like in which leukocyte invasion participates in gastrointestinal tract and other epithelial tissue (for example skin, urethra, trachea, articulation synovial membrane). The composition of this invention is further useful in therapy of pathological state in which leukocyte invasion participates in the tissue other than epithelial tissue such as lung, blood vessel, heart and nervous system or the like and transplanted organ such as kidney, liver, pancreas and heart or the like.

(0002)

Technology of the Prior Art

The adhesion of leukocyte to endothelial cell or extracellular matrix protein is a main process of immunity and inflammation, and plurality of adhesion interactions are involved. The first phenomenon of this process is rolling of leukocyte by change of integrin avidity (affinity), and this becomes the strong adhesion that is formed next (cf. Butcher, Cell, 67: 1033-1036 (1991), Haalan, Blood, 3: 513-525 (1985), Hemler, Annu. Rev. Immunol. 8: 365-400 (1990), Osborne, Cell, 62: 3-6 (1990), Smith et al., Immunol, Rev. 114: 109-143 (1990), Springer, Nature, 346= 425-434 (1990), Springer, Cell, 76: 301-314 (1994)). In response to chemotactic factor, the leukocyte emigrates to the tissue partially comprising extracellular matrix protein fibronectin (FN) (cf. Winer et al., J. Cell Biol. 105: 1873-1884 (1987)) and collagen (CN) (cf. Bornstein et al., Ann, Rev, Biochem. 49: 957-1003 (1980) and Miller, K.A. Piers and A.H. Ledge eds, Connective Tissue Biochemistry, "chemistry of collagen and its distribution", Euseviel publication, Amsterdam, 41-78 (1983)) through two adjacent endothelial cells. The important recognition molecule participating in these reactions belongs to integrin gene superfamily (cf. Hemler, Annu, Rev, Immunol. 8: 365-400 (1990), Highness, Cell, 48: 549-554 (1987), Shimizu et al., Immunol, Rev. 114: 109-143 (1990) and Springer, Nature, 346: 425-434 (1990)).

(0003)

The integrin is constructed from the subunits called α (α) and β (β) subunits which are gathered with non-covalent bond (cf. Helmer, Annu, Rev, Immunol. 8: 365-400 (1990), Highness, Cell, 48,549-554 (1987), Shimizu et al., Immunol, Rev. 114: 109-143 (1990), Springer, Nature, 346: 425-434 (1990)). At present, 8 integrin β subunits have been identified which bind to 16 different α subunits and form 22 different integrins. The β 7 integrin subunit which was first cloned by Eel et al. (Eel et al., J. Biol. Chem. 266: 11009-11016 (1991)) is expressed only on the leukocyte, and is known to bond with two different α subunits, α4 (Rieug et al., J. Cell, Biol. 117: 179-189 (1992)) and αE (Sarfurbensussan et al., Eur. J. Immunol. 22: 273-277 (1992) and Carshew et al., Eur. J. Immunol. 21: 2591-2597 (1991)). The αE β7 heterodimer has E-cadherin as the sole ligand thereof.

(0004)

The α4 β7 complex has 3 known ligands (VCAM, CS-1, MAdCAM). The ligand showing specificity only with respect to α 4 β 7 is mucosal addressing cell adhesion molecule (MAdCAM)) (cf. Andrew et al., J. Immunol. 153: 3847-3861 (1994), Briskin et al., Nature, 363: 461-464 (1993) and Shajean et al., J. Immunol. 156: 2851-2857 (1996)). MAdCAM is mostly expressed on aggregated lymphatic follicle high endothelial venule in mesenteric lymph node and also on gastrointestinal tract basal membrane and mammary gland small vein (Berg et al., Immunol, Rev. 105: 5 (1989)). The integrin α 4 β 7 and MAdCAM have been shown to be important in the regulation of leukocyte migration to normal intestine (Bolzman et al., Cell 56: 37 (1989)). The second ligand of α4 β7 is connecting segment 1 (CS-1), which is another splicing region of FNA chain (cf. Guang et al., Cell, 60: 53-61 (1990) and Weiner et al., J. Cell Biol. 109: 1321-1330 (1989)). The cell binding site within this separately spliced region comprises 25 amino acids, and the carboxyl terminal amino acid residues thereof, EILDVPST form the recognition motif (MOTIF) (cf. Komoriya, J. Biol. Chem. 266: 15075-15079 (1991) and Weiner et al., J. Cell. Biol. 116: 489-497 (1992)).

(0005)

The third ligand of α4 β7 is vascular cell adhesion molecule-1(VCAM-1) which is a cytokine inducible protein expressed on endothelial cell (cf. Ericess et al., Cell, 60: 577-584 (1990) and Rieug et al., J. Cell Biol. 117: 179-189 (1992)). The VCAM and CS-1 (c. Ericess et al., Cell, 60: 577-584 (1990)) are 2 ligands which are common to α 4 β 7 and α 4 β 1. Whether the MAdCAM, VCAM and CS-1 bind to the same site on α 4 β 7 or not is not clear. Using a panel of monoclonal antibodies, Andrew et al. showed that different but overlapped epitopes are involved in the interaction of α 4 β 7 with three different ligands (cf. Andrew et al., J. Immunol, 153: 3847-3861 (1994)).

(0006)

From many in vitro and in vivo studies, the α 4 is demonstrated to have an important role in the cause of many diseases. Monoclonal antibody with respect to α4 is investigated in various disease models. The effectiveness of anti-α4 antibody has been shown experimental autoimmune type encephalomyelitis models in rat and mouse (cf. Baron et al., J. Exp, Med. 177: 57-68 (1993) and Ednock et al., Nature, 356: 63-66 (1992)). A number of studies evaluated the role of α4 in allergic bronchitis (cf. Abraham et al., J. Clin, Invest. 93: 776-787 (1994), Bockner et al., J. Exp, Med. 173: 1553-1556 (1991), Walsh et al., J. Immunol, 146: 3419-3423 (1991) and Wegg et al., J. Exp, Med. 177: 561-566 (1993)). For example, monoclonal antibody of α4 was effective in some lung antigen attack models (cf. Abraham et al., J. Clin. Invest. 93: 776-787 (1994) and Wegg et al., J. Exp, Med. 177: 561-566 (1993)). Interestingly, disturbance of cells recruitment is not found in certain type of lung models despite that fact that the exclusion of delayed type response is present (cf. Abraham et al., J. Clin, Invest. 93: 776-787 (1994)). When anti-α4 antibody was administered, the cotton-top tamarin which develops spontaneous chronic colitis showed a significant reduction of colitis (cf. Bell et al., J. Immunol. 151: 4790-4802 (1993) and Podolski et al., J. Clin, Invest. 92: 372-380 (1993)). Monoclonal antibody with respect to α 4 hinders insulitis, and delays the onset of diabetes in non-obese diabetic mouse model (cf. Baron et al., J. Clin, Invest. 93: 1700-1708 (1994), Barcley et al., Diabetes, 43: 529-534 (1994) and Yang et al., Proc. Natl. Acad. Sci. USA, 90: 10494-10498 (1993)). As the other diseases involving α4, rheumatoid arthritis (cf. Lahon et al., J. Clin, Invest. 88: 546-552 (1991) and Morales-Dukret et al, J. Immunol. 149: 1424-1431 (1992)) and arteriosclerosis (cf. Tiblsky et al., Science, 251: 788-791(1991)) may be proposed. The delayed type hypersensitivity reaction (cf. Isseks, J. Immunol. 147: 4178-4184 (1991)) and contact hypersensitivity reaction (cf. Quixolm et al., Eur, J. Immunol. 23: 682-688 (1993) and Fargson et al., J. Immunol. 150; 1172-1182 (1993)) are also disrupted by anti α 4 antibody. Cf. Rob et al. J. Clin. Invest. 94: 1722-1728 (1995) for excellent discussion on the in vivo studies of α 4 in diseases.

(0007)

These studies clearly define the involvement of α 4 in various diseases, however, whether the observed inhibition was due to blocking of α 4 β 1, α 4 β 7 or both is not clear. Recently, several studies have looked at this point using antibody recognises α4 β7 complex (cf. Hesterburgh et al., Gastroenterology (1997)), antibody with respect to β7 or antibody with respect to MAdCAM which does not bind to α4 β1 (cf. Piccallera et al, J. Immunol. 158: 2099-2106 (1997)). In primate model of inflammation bowel disease, antibody with respect to α4 β7 complex was found to improve inflammation and to decrease diarrhea (cf. Hesterberg et al., Gastroenterology, 111: 1373-1380 (1996)). In another model, monoclonal antibody with respect to β7 or MAdCAM blocked the recruitment of leukocyte to colon, and decreased the degree of inflammation in colon of severe combined immunodeficiency mouse (scid mice) reconstituted with CD45RBhighCD4+ cells (cf. Piccallera et al., J. Immunol. 158: 2099-2106 (1997)). This suggests that, together with

the fact that gastrointestinal tract assembly lymphoid tissue is severely damaged in β7 deficient mouse, the α4 β7 is an important mediator of the inflammatory bowel disease.

(0008)

The expression of α4 β7 on various leukocytes and the increase of α4 β7 positive cells in onset tissue mean the receptor plays an important role in the cell recruitment to other inflammatory sites in addition to the migration to intestine. The CD4+, CD8+, T cells, B cells, NK cells and eosinophils from human peripheral blood were shown to express α4 β7 at high levels (cf. Piccallera et al., J. Immunol. 158: 2099-2106 (1997)). An increase of α4 β7 expression T cells was observed in synovial membrane of rheumatoid arthritis patient, and it was predicted that the increase of α4 β7 expression contributes to deterioration and perpetuation of this disease (cf. Lazalovich et al., J. Immunol. 151: 6482-6489 (1993)). In non-obesity diabetes mellitus mouse, MAdCAM is expressed on high endothelial venule of inflammation Langerhans' islet in pancreas, and this suggests a role of α4 β7 in diabetes mellitus (cf. Kelner et al., Science, 266: 1395-1399 (1994)). The distribution of α4 β7 on lymphocyte and eosinophil (Eel et al., J. Immunol. 153: 517-528 (1994)) and the results of in vitro study showing that α4 β7 mediates the adhesion of human eosinophil to VCAM, CS-1 and MAdCAM, both indicate that this integrin is a target molecule in asthma. These data suggest that the integrin α4 β7 plays an important role in various inflammation diseases.

(0009)

The N-terminal domain of MAdCAM (domain 1) displays monology to the N-terminal integrin recognition domains of both VCAM and ICAM (cf. Briskin et al., Nature, 363: 461-464 (1993)). Using the site directive mutagenicity of MAdCAM, the binding motif was identified in the domain 1 as 3 amino acid residues within C-D loop (cf. Viney et al., J. Immunol. 157: 2488-2497 (1996)). The mutation of L40, D41 and T42 results in complete loss of binding ability to α4 β7, and this indicates that LDT on MAdCAM is involved in the binding loop (cf. Viney et al., J. Immunol. 157: 2488-2497 (1996)). By combination of this region on MAdCAM and other integrin ligands such as VCAM or CS-1 or the like, the presence of conserved binding motif or consensus sequence consisting of G / Q, I / L, E / D, T / S and P / S residue is shown (cf. Briskin et al., J. Immunol. 156: 719-726 (1996)). This is further supported from the fact that it was shown that the linear or cyclic peptide of LDT component blocked the cell adhesion to MAdCAM in vitro (cf. Shellof et al., Bioorganic & Medicinal Chemistry Letters, 6: 2495-2500 (1996) and Viney et al., J. Immunol. 157= 2488-2497 (1996)).

(0010)

Problems to be Overcome by this Invention

By the use of monoclonal antibody with respect to integrin in vivo, many integrins are shown to

be effective therapeutic targets in practice for inflammation and heart angiopathy and organ transplantation. The objective of this invention is to put forward a medicinal composition containing, as effective component, a non-peptide small molecule α4 antagonist, which can be bioavailable by oral administration. A medicinal composition containing, as effective component, a potent inhibitor of α 4-mediated adhesion to either MAdCAM, VCAM or CS-1, which is a small molecule and is useful for the therapy of inflammatory diseases, is put forward.

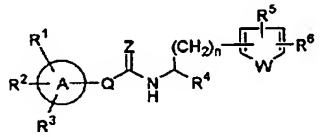
(0011)

Means to Overcome these Problems

These inventors carried out assiduous investigations in order to solve the problem, as a result discovered novel medicinal compositions containing the compound which was α4 (including α4 β7)-mediated cell adhesion inhibitor. This invention was completed as a result of this.

(0012)

In other words, this invention relates to a pharmacological composition containing a compound represented by formula (I)



(I)

or its pharmacologically acceptable salt.

In the formula, ring A is aromatic hydrocarbon ring or heterocyclic ring,

Q is bond; carbonyl group; lower alkylene group which may be substituted by hydroxy group or phenyl group; lower alkenylene group; or -O-(lower alkylene)-group,

n is an integer of 0, 1 or 2,

W is oxygen atom, sulfur atom, -CH=CH- group or -N=CH- group,

Z is oxygen atom or sulfur atom,

R1, R2 and R3 may be the same or different and denote a group selected from the following groups,

a) a hydrogen atom,

b) a halogen atom,

c) a substituted- or unsubstituted-lower alkyl group,

d) a substituted- or unsubstituted-lower alkoxy group,

e) a nitro group,

f) a substituted- or unsubstituted-amino group,

g) a carboxyl group or ester or amide thereof,

h) a cyano group,

i) a lower alkyl thio group,

j) a lower alkane sulphonyl group,

k) a substituted- or unsubstituted-sulphamoyl group,

l) a substituted- or unsubstituted-aryl group,

m) a substituted- or unsubstituted-heterocyclic group and

n) hydroxy group, or two of R1, R2 and R3 may bond together at the terminals thereof and may form a lower alkylene dioxy group,

R4 is tetrazolyl group, carboxyl group, or amide or ester thereof

R5 is a group selected from the following groups

a) a hydrogen atom,

b) a nitro group,

c) a substituted- or unsubstituted-amino group,

d) a hydroxy group,

e) a lower alkanoyl group,

f) a substituted- or unsubstituted-lower alkyl group,

g) a lower alkoxy group,

h) a halogen atom and

i) 2-oxo pyrrolidinyl group,

R6 is a group selected from the following groups

a) a substituted- or unsubstituted-phenyl group and

b) a substituted- or unsubstituted-heteroaryl group.

(0013)

A composition of this invention is useful in the prevention and treatment of pathosis due to α 4 (α 4 β 7 and α 4 β 1 are included) interstitial cell adhesion.

(0014)

Effective component of this invention may be present as optically active isomer based on asymmetric carbon thereof, and this invention includes isomers thereof and mixture thereof.

(0015)

Conditions for Carrying out this Invention

The following abbreviations used through this specification have the following meanings respectively.

BOP-Cl= bis(2-oxo-3-oxazolidinyl)phosphonic acid chloride

BOP reagent= Benzotriazol-1-yloxy-tris (dimethylamino) phosphonium hexafluorophosphate

DCC= 1,3-dicyclohexylcarbodiimide

EDC= 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide

THF= tetrahydrofuran

DMF= N,N-dimethylformamide

DIEA= diisopropyl ethylamine

DMAP= 4-(N,N-dimethylamino) pyridine

DBU= 1,8-diazabicyclo[5.4.0] undec-7-ene

CDI= carbonyldiimidazole

HOBT= 1-hydroxybenzotriazole

BOC= tert butoxycarbonyl

Tf2O= anhydrous trifluoromethanesulfonic acid

Tf= trifluoromethane sulfonyl group

TFA= trifluoroacetic acid

DME= 1,2-dimethoxyethane

MsCl= methanesulfonyl chloride

DIAD= diisopropyl azo dicarboxylate

Ac= acetyl group

Me= methyl group

Et= ethyl group

Ph= phenyl group

Bn= benzyl group

EtOAc= ethyl acetate (AcOEt)

mCPBA=m-chloroperbenzoic acid

TMS= trimethylsilyl group

h= hour

min= minute

saturated.= saturated

(0016)

Moreover, the following various terms are used with the specific meaning and interpretation such as is described hereinafter. "Lower" used preceding alkyl, alkoxy, alkylene or alkane denotes that it includes a straight chain or branched chain of 1-6 carbon atoms, and "lower" used preceding alkanoyl, alkenyl or alkenylene denotes that it includes a straight chain or branched chain of 2-7 carbon atoms. "Lower" used preceding cycloalkyl or cycloalkoxy denotes that it includes a straight chain or branched chain of 3-7 carbon atoms.

(0017)

As for the term such as "morpholino lower alkyl", "hydroxy lower alkoxy" or the like, functional group before "lower" denotes that it is functional group substituent connected to "lower". For example, "hydroxy lower alkoxy" denotes a lower alkoxy group containing at least one hydroxy substituent.

(0018)

Term such as for example "lower alkyl group substituted by halogen atom", "phenyl group substituted by lower alkoxy group" or the like denotes functional group including at least one substituent. For example, as "lower alkyl group substituted by halogen atom", lower alkyl group containing at least one halogen atom is denoted, as "phenyl group substituted by lower alkoxy group", phenyl containing at least one lower alkoxy group is denoted.

Moreover, through interpretation of usage of this type by technical people of this field, several different nomenclatures in this type of nomenclature and combinations of this type of nomenclatures may also may be interpreted within the range of normal interpretation of technical people of the appropriate field. Accordingly, this type of nomenclature is not one which is applied to molecules such as ones which cannot exist, or combinations of substituents which cannot be formed.

(0019)

As embodiment of this invention, configuration of the compound is not restricted. The compound of this invention may be single configuration or the compounds of a mixture of several different configurations.

(0020)

The "aromatic hydrocarbon ring" in the aforesaid formula (I), is a monocyclic, bicyclic or tricyclic aromatic hydrocarbon ring such as for example benzene ring, naphthalene ring, anthracene ring, fluorene ring or the like.

(0021)

The "heterocycle" in the aforesaid formula (I), is monocyclic, bicyclic or tricyclic containing heteroatom. For example, it is a pyridine ring, pyrimidine ring, pyridazine ring, pyrazine ring, quinoline ring, isoquinoline ring, quinazoline ring, phthalazine ring, imidazole ring, isoxazole ring, pyrazole ring, oxazole ring, thiazole ring, indole ring, benzazole ring, benzothiazole ring, benzimidazole ring, benzofuran ring, furan ring, thiophene ring, oxadiazole ring, thiadiazole ring, triazole ring, tetrazole ring, pyrrole ring, indoline ring, indazole ring, iso indole ring, purine ring, morpholine ring, quinoxaline ring, benzothiophene ring, pyrrolidine ring, benzofurazan ring, benzothiadiazole ring, thiazolidine ring, imidazo thiazole ring, dibenzofuran ring and isothiazole ring.

(0022)

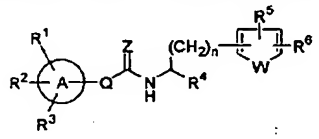
As "aryl group" in the aforesaid formula (I), monocyclic, bicyclic or tricyclic aromatic group is meant, and examples include phenyl group, naphthyl group, anthryl group and fluorenyl group.

(0023)

As "heterocyclic group" in the aforesaid formula (I), heteroatom of nitrogen atom, oxygen atom and sulfur atom is contained, and monocyclic, bicyclic or tricyclic group is denoted. For example, it is pyridyl group, pyrimidinyl group, pyridazinyl group, pyrazinyl group, quinolyl group, isoquinolyl group, quinazolinyl group, phthalazinyl group, imidazolyl group, isoxazolyl group, pyrazolyl group, oxazolyl group, thiazolyl group, indolyl group, benzazolyl group, benzothiazolyl group, benzimidazolyl group, benzofuranyl group, furyl group, thienyl group, pyrrolyl group, oxadiazolyl group, thiadiazolyl group, triazolyl group, tetrazolyl group, indolinyl group, indazolyl group, isoindolyl group, purinyl group, morpholinyl group, quinoxalinyl group, benzothienyl group, pyrrolidinyl group, benzofurazanyl group, benzothiadiazolyl group, thiazolidinyl group, imidazo thiazolyl group, dibenzofuranyl group, isothiazolyl group, pyrrolinyl group, piperidinyl group, piperazinyl group and tetrahydropyranyl group. "Heteroaryl group" in the aforesaid formula (I) contains heteroatom of nitrogen atom, oxygen atom and sulfur atom, and monocyclic, bicyclic or tricyclic aromatic group is denoted and is "the aforesaid heterocyclic group" other than for example pyrrolidinyl group, pyrrolinyl group, piperidinyl group, piperazinyl group, morpholinyl group, tetrahydropyranyl group. Preferred "heteroaryl groups" are pyridyl group, thienyl group, benzofuranyl group, pyrimidyl group and isoxazolyl group.

(0024)

In the compound (I) of this invention, new compounds are the following.



(I)

In the formula, ring A is aromatic hydrocarbon ring or heterocyclic ring,

Q is bond; carbonyl group; lower alkylene group which may be substituted by hydroxy group or phenyl group; lower alkenylene group; or -O-(lower alkylene)-group,

n is an integer of 0, 1 or 2,

W is oxygen atom, sulfur atom, -CH=CH- group or -N=CH- group,

Z is oxygen atom or sulfur atom,

R1, R2 and R3 may be the same or different and denote a group selected from the following groups,

a) a hydrogen atom,

b) a halogen atom,

c) a substituted- or unsubstituted-lower alkyl group,

d) a substituted- or unsubstituted-lower alkoxy group,

e) a nitro group,

f) a substituted- or unsubstituted-amino group,

g) a carboxyl group or ester or amide thereof,

h) a cyano group,

i) a lower alkyl thio group,

j) a lower alkane sulphonyl group,

k) a substituted- or unsubstituted-sulphamoyl group,

l) a substituted- or unsubstituted-aryl group,

m) a substituted- or unsubstituted-heterocyclic group and

n) hydroxy group, or two of R1, R2 and R3 may bond together at the terminals thereof and may form a lower alkylene dioxy group,

R4 is tetrazolyl group, carboxyl group, or amide or ester thereof

R5 is a group selected from the following groups

a) a hydrogen atom,

b) a nitro group,

c) a substituted- or unsubstituted-amino group,

d) a hydroxy group,

e) a lower alkanoyl group,

f) a substituted- or unsubstituted-lower alkyl group,

g) a lower alkoxy group,

h) a halogen atom and

i) 2-oxo pyrrolidinyl group,

R6 is a group selected from the following groups

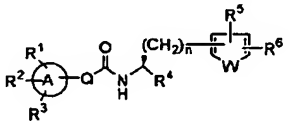
a) a substituted- or unsubstituted-phenyl group and

b) a substituted- or unsubstituted-heteroaryl group.

Provided that, when ring A is a benzene ring, its 3 position and 5 position, or its 2 position and 4 position, are not substituted by methyl group, or the pharmacologically acceptable salts thereof.

(0025)

Preferred configuration of effective component of this invention is represented by formula (I-A).



(I-A)

(wherein, symbol are the same as above-mentioned).

(0026)

Preferred embodiment of this invention is the compound of formula (I) wherein, when ring A is benzene ring, one of 2-position thereof or 6-position is substituted.

(0027)

Another preferred embodiment of the invention is a compound of formula (I) wherein R1, R2 and R3 are groups selected from the following group.

a) a hydrogen atom,

b) a halogen atom,

c) a substituted- or unsubstituted-lower alkoxy group,

d) a nitro group,

e) a substituted- or unsubstituted-amino group,

f) a carboxyl group or ester or amide thereof,

g) a cyano group,

h) a lower alkyl thio group,

i) a lower alkane sulphonyl group,

j) a substituted- or unsubstituted-sulphamoyl group,

k) a substituted- or unsubstituted-aryl group,

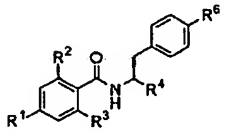
l) a substituted- or unsubstituted-heterocyclic group and

m) hydroxy group, or two of R1, R2 and R3 may bond together at the terminals thereof and may form a lower alkylene dioxy group,

(0028)

A further preferred embodiment of effective component of this invention is the compound represented by following formula (I-B) .

(0029)



(I-B)

(wherein, symbol are the same as above-mentioned).

(0030)

In a further preferred embodiment of effective component of this invention, R1 is hydrogen atom, halogen atom, carboxyl group, carbamoyl group, nitro group, a substituted- or unsubstituted-amino group, or a substituted- or unsubstituted-heterocyclic group, R2 is a hydrogen atom, lower alkyl group or halogen atom, R3 is a hydrogen atom, lower alkyl group or halogen atom and R6 is a phenyl group optionally substituted at the 2-position, 4 position and/or 6-position by a group selected from the following group, 1) halogen atom, 2) substituted or unsubstituted lower alkoxy group, 3) substituted or unsubstituted lower alkyl group, 4) substituted or unsubstituted amino group, 5) substituted or unsubstituted carbamoyl group and 6) substituted or unsubstituted sulphamoyl group.

(0031)

In furthermore preferred embodiment of this invention, R6 is a phenyl group which is optionally substituted by 1-3 groups selected from the following group.

1) The lower alkoxy group and 2) lower alkyl group which may be substituted by group selected from the substituted or unsubstituted amino group, substituted or unsubstituted piperidinyl group, substituted or unsubstituted morpholino group, substituted or unsubstituted piperazinyl group, substituted or unsubstituted pyrrolidinyl group and substituted or unsubstituted imidazolidinyl group.

(0032)

In another embodiment of this invention, ring A is benzene ring, pyridine ring, pyrazine ring, furan ring, isoxazole ring, benzofuran ring, thiophene ring, pyrrole ring or indole ring, R1, R2 and R3 are the group which is selected from the following group.

a) a hydrogen atom,
b) a halogen atom,
c) a lower alkyl group optionally substituted by halogen atom or halobenzoylamino group,
d) a lower alkoxy group optionally substituted by halogen atom,
e) a nitro group,
f) an amino group which may be substituted by one or two groups selected from 1) a lower alkyl group, 2) a lower alkanoyl group, 3) a halo benzoyl group, 4) a lower alkoxycarbonyl group, 5) a lower alkane sulphonyl group optionally substituted by halogen atom, 6) a benzenesulfonyl group optionally substituted by lower alkyl group, trihalo lower alkyl group, halogen atom or lower alkoxy group, 7) a thiophene sulphonyl group, 8) a carbamoyl group optionally substituted by lower alkyl group or lower alkyl phenyl group, 9) a thiocarbamoyl group optionally substituted by lower alkyl group, phenyl group or phenyl lower alkyl group, 10) a thiazolinyl group and 11) a sulphamoyl group optionally substituted by lower alkyl group,
g) a carboxyl group,
h) a carbamoyl group optionally substituted by lower alkane sulphonyl group,
i) a lower alkoxycarbonyl group,
j) a cyano group,
k) a lower alkyl thio group,
l) a lower alkane sulphonyl group,
m) a sulphamoyl group,
n) a phenyl group,
o) a pyrrolidinyl group optionally substituted by oxo group,

p) a pyrrolyl group optionally substituted by the group which is selected from 1) a lower alkanoyl group optionally substituted by a halogen atom, 2) a halogen atom, 3) a formyl group and 4) a lower alkyl group optionally substituted by hydroxy group,

q) a thienyl group,

r) an isoxazolyl group optionally substituted by lower alkyl group,

s) a thiazolyl group,

t) a pyrazolyl group,

u) a pyrazinyl group,

v) a pyridyl group and

w) a hydroxy group,

R4 is a group selected from the following groups,

a) a carboxyl group,

b) a lower alkoxycarbonyl group optionally substituted by 1) a pyridyl group or 2) an amino group optionally substituted by lower alkyl group,

c) a lower cycloalkoxycarbonyl group,

d) a carbamoyl group optionally substituted by hydroxy group or lower alkane sulphonyl group and

e) a tetrazolyl group,

R5 is a group selected from the following groups,

a) a hydrogen atom,

b) a nitro group,

c) an amino group optionally substituted by lower alkanoyl group, lower alkoxycarbonyl group or lower alkane sulphonyl group,

d) a hydroxy group,

e) a lower alkanoyl group,

f) a lower alkyl group optionally substituted by 1) a hydroxy group or 2) imino group substituted by hydroxy group or lower alkoxy group,

g) a lower alkoxy group,

h) a halogen atom and

i) a 2-oxo pyrrolidinyl group,

R6 is a group selected from the following groups,

a) a phenyl group optionally substituted by 1-5 groups selected from the following groups,

1) a halogen atom,

2) a nitro group,

3) a formyl group,

4) a hydroxy group,

5) a carboxyl group,

6) a lower alkoxy group optionally substituted by the group which is selected from i) a carboxyl group or an amide or ester thereof, ii) a hydroxy group, iii) a cyano group, iv) a halogen atom, v) an amino group optionally substituted by lower alkyl group, vi) a pyridyl group, vii) a thiazolyl group optionally substituted by lower alkyl group, viii) an isoxazolyl group optionally substituted by lower alkyl group, ix) a piperidyl group optionally substituted by lower alkyl group, x) a pyrrolidinyl group optionally substituted by lower alkyl group, xi) a phenyl group optionally substituted by halogen atom, xii) a furyl group, xiii) a thienyl group and xiv) a lower alkoxy group,

7) a lower alkyl group optionally substituted by a group selected from i) a halogen atom, ii) a hydroxy group, iii) a carboxyl group or an amide or ester thereof, iv) a lower alkoxy group, v) an amino group optionally substituted by 1-2 groups selected from the lower alkyl group, hydroxy lower alkyl group, lower alkyl amino lower alkyl group, phenyl lower alkyl group, phenyl group and pyridyl group, vi) a piperidinyl group optionally substituted by lower alkylene dioxy group, oxo group or hydroxy group, vii) a morpholino group optionally substituted by lower alkyl group, viii) a thio morpholino group which may be oxidised, ix) a piperazinyl group optionally substituted by lower alkyl group, hydroxy lower alkyl group, lower alkanoyl group or phenyl lower alkyl group, x) a pyrrolidinyl group optionally substituted by oxo group and xi) an imidazolidinyl group optionally substituted by 1-3 groups selected from lower alkyl group and oxo group,

8) a lower alkenyl group optionally substituted by carboxyl group or amide or ester thereof,

9) an amino group optionally substituted by the group selected from i) a phenyl group, ii) a lower alkoxycarbonyl group, iii) a lower alkane sulphonyl group, iv) a carbamoyl group optionally substituted by lower alkyl group or lower alkyl phenyl group, v) a lower alkanoyl group, vi) a lower alkyl group, vii) a lower alkenyl group and viii) a thiocarbamoyl group optionally substituted by lower alkyl group,

10) a carbamoyl group optionally substituted by lower alkyl group, hydroxy lower alkyl group, morpholino lower alkyl group, phenyl lower alkyl group or lower alkane sulphonyl group,

11) a sulphamoyl group optionally substituted by the group selected from i) a lower alkyl group, ii) a benzoyl group, iii) a lower alkoxycarbonyl group and iv) a lower alkanoyl group,

12) a lower alkenyloxy group,

13) a lower alkylene dioxy group,

14) a piperazinyl carbonyl group optionally substituted by lower alkyl group,

15) a lower alkanoyl group,

16) a cyano group,

17) a lower alkyl thio group,

18) a lower alkane sulphonyl group,

19) a lower alkyl sulfinyl group and

20) a group represented by formula –(CH2)q-O- (wherein, q is an integer of 2 or 3),

b) a pyridyl group optionally substituted by lower alkyl group,

c) a thienyl group optionally substituted by the group selected from the following groups,

1) a halogen atom,

2) a lower alkyl group optionally substituted by hydroxy group,

3) a cyano group,

4) a formyl group,

5) a lower alkoxy group and

6) a lower alkanoyl group,

d) a benzofuranyl group,

e) a pyrimidinyl group optionally substituted by lower alkoxy group,

f) an isoxazolyl group optionally substituted by lower alkyl group and

g) a pyrrolyl group optionally substituted by lower alkoxycarbonyl group.

(0033)

In preferred embodiment of this invention, ring A is a benzene ring, Q is a bond, W is CH=CH-, R1 is a group which is selected from the following group.

a) a hydrogen atom,

b) a halogen atom,

c) a lower alkyl group,

d) a lower alkoxy group,

e) a nitro group,

f) an amino group optionally substituted by a group selected from 1) a lower alkyl group, 2) a lower alkanoyl group, 3) a lower alkoxycarbonyl group, 4) a lower alkane sulphonyl group optionally substituted by halogen atom, 5) a benzenesulfonyl group optionally substituted by lower alkyl group, trihalo lower alkyl group, halogen atom or lower alkoxy group, 6) a thiophene sulphonyl group, 7) a carbamoyl group optionally substituted by lower alkyl group or lower alkyl phenyl group, 8) a thiocarbamoyl group optionally substituted by lower alkyl group and 9) a sulphamoyl group optionally substituted by lower alkyl group,

g) a carboxyl group,

h) a carbamoyl group optionally substituted by lower alkane sulphonyl group,

i) a lower alkane sulphonyl group,

j) a sulphamoyl group,

k) a phenyl group,

l) a pyrrolidinyl group optionally substituted by oxo group,

l) a pyrrolyl group optionally substituted by lower alkyl group,

m) a thienyl group,

n) an isoxazolyl group optionally substituted by lower alkyl group,

o) a thiazolyl group,

p) a pyrazolyl group,

q) a pyrazinyl group,

r) a pyridyl group and

s) a hydroxy group,

R2 is a hydrogen atom or halogen atom, R3 is a hydrogen atom or halogen atom, R4 is a) a carboxyl group, b) a lower alkoxycarbonyl group optionally substituted by lower alkyl amino group or c) a carbamoyl group optionally substituted by a lower alkane sulphonyl group, R5 is a group selected from the following groups,

a) a hydrogen atom,

b) an amino group optionally substituted by lower alkanoyl group, lower alkoxycarbonyl group or lower alkane sulphonyl group,

c) a lower alkanoyl group,

d) a lower alkyl group optionally substituted by 1) a hydroxy group or 2) imino group substituted by hydroxy group or lower alkoxy group,

e) a lower alkoxy group and

f) a halogen atom,

R6 is a phenyl group optionally substituted by 1-5 groups selected from the following groups

a) a halogen atom,

b) a formyl group,

c) a hydroxy group,

d) a lower alkoxy group optionally substituted by 1) a carboxyl group, 2) a hydroxy group, 3) a cyano group, 4) a halogen atom, 5) an amino group optionally substituted by lower alkyl group, 6) a pyridyl group, 7) a phenyl group, 8) a thienyl group or 9) a lower alkoxy group,

e) a lower alkyl group optionally substituted by 1) an amino group optionally substituted by lower alkyl group, hydroxy lower alkyl group, lower alkyl amino lower alkyl group or phenyl group, 2) a piperidinyl group optionally substituted by lower alkylene dihydroxy group, 3) a morpholino group optionally substituted by lower alkyl group, 4) a thio morpholino group in which sulfur atom may be oxidised, 5) a piperazinyl group optionally substituted by lower alkyl group, hydroxy lower alkyl group, lower alkanoyl group or phenyl lower alkyl group, 6) a pyrrolidinyl group optionally substituted by oxo group or 7) an imidazolidinyl group optionally substituted by 1-3 groups selected from the oxo group and lower alkyl group,

f) an amino group optionally substituted by 1) a lower alkoxycarbonyl group, 2) a lower alkane sulphonyl group, 3) a carbamoyl group optionally substituted by lower alkyl group or lower alkyl phenyl group, 4) a lower alkanoyl group, 5) a lower alkyl group, 6) a lower alkenyl group or 7) a thiocarbamoyl group optionally substituted by lower alkyl group,

g) a carbamoyl group optionally substituted by 1) a lower alkyl group, 2) a hydroxy lower alkyl group, 3) a morpholino lower alkyl group, 4) a phenyl lower alkyl group or 5) a lower alkane sulphonyl group,

h) a sulphamoyl group optionally substituted by lower alkyl group,

i) a lower alkenyloxy group,

j) a lower alkylene dihydroxy group,

k) a cyano group,

l) a lower alkyl thio group and

m) a lower alkane sulphonyl group.

(0034)

In preferred embodiment of this invention, R1 is 1) a hydrogen atom, 2) a halogen atom, 3) a lower alkanoyl amino group, 4) a lower alkoxycarbonylamino group, 5) a lower alkane sulfonyl amino group optionally substituted by halogen atom, 6) a benzensulphonyl amino group optionally substituted by lower alkyl group, trihalo lower alkyl group, halogen atom or lower alkoxy group, 7) a thiophene sulfonyl amino group, 8) an ureide group optionally substituted by lower alkyl group or lower alkyl phenyl group, 9) a lower alkyl thiouredide group or 10) a lower alkyl sulphamoyl amino group,

R2 is a halogen atom,

R3 is a hydrogen atom or halogen atom,

R6 is a phenyl group optionally substituted by 1-3 groups selected from 1) a lower alkoxy group, 2) a lower alkyl group optionally substituted by 1-3 groups selected from the lower alkyl amino group, hydroxy lower alkyl amino group, lower alkyl amino lower alkyl amino group, piperidinyl group, lower alkyl piperidinyl group, morpholino group, lower alkyl morpholino group, thio morpholino group, piperazinyl group, lower alkyl piperazinyl group, lower alkanoyl piperazinyl group and pyrrolidinyl group, 3) a sulphamoyl group optionally substituted by lower alkyl group and 4) a carbamoyl group optionally substituted by lower alkyl group.

(0035)

With furthermore preferred embodiment of this invention R1 hydrogen atom, R3 halogen atom R6 is 2-lower alkyloxyphenyl group, 2,6-dilower alkyloxyphenyl group, 2,6-dilower alkoxy-4-[(N, N-dilower alkyl amino) lower alkyl] phenyl group, 2,6-dilower alkoxy-4-[(4-lower alkyl-1-piperazinyl) lower alkyl] phenyl group, 2,6-dilower alkoxy-4-[1-piperidinyl lower alkyl] phenyl group, 2,6-dilower alkoxy-4-[N, N-di (lower alkyl) carbamoyl] phenyl group or 2,6-dilower alkoxy-4-[(morpholino) lower alkyl] phenyl group.

(0036)

In furthermore preferred embodiment of this invention, lower alkoxy is methoxy.

(0037)

As effective component of this invention, the preferred compound is N-(2,6-dichlorobenzoyl)-4-(2,6-dimethoxyphenyl)-L-phenylalanine, N-(2,6-dichlorobenzoyl)-4-[2,6-dimethoxy-4-(1-piperidinomethyl) phenyl]-L-phenylalanine, N-(2,6-dichlorobenzoyl)-4-[2,6-dimethoxy-4-[(4-methyl piperazinyl) methyl] phenyl]-L-phenylalanine, N-(2,6-dichlorobenzoyl)-4-[2,6-dimethoxy-4-(morpholinomethyl) phenyl]-L-phenylalanine, N-(2,6-dichlorobenzoyl)-4-[2,6-dimethoxy-4-[(N,N-dimethylamino) methyl] phenyl]-L-phenylalanine, N-(2,6-dichlorobenzoyl)-4-[2,6-dimethoxy-4-(N,N-dimethylcarbamoyl) phenyl]-L-phenylalanine, N-(2,6-dichloro-4-hydroxybenzoyl)-4-(2,6-dimethoxyphenyl)-L-phenylalanine, N-(2,6-dichlorobenzoyl)-4-(2-ethoxy-6-methoxyphenyl)-L-phenylalanine, N-(2,6-difluorobenzoyl)-4-(2,6-dimethoxyphenyl)-L-phenylalanine, N-(2,6-dichlorobenzoyl)-4-(2,3-methylenedioxy-6-methoxyphenyl)-L-phenylalanine, N-(2,6-dichlorobenzoyl)-3-(1-hydroxyethyl)-4-(2,6-dimethoxyphenyl)-L-phenylalanine, N-(2,6-dichlorobenzoyl)-4-(2,4,6-trimethoxyphenyl)-L-phenylalanine, N-[2,6-dichloro-4-[(trifluoromethane sulfonyl) amino] benzoyl]-4-(2,6-dimethoxyphenyl)-L-phenylalanine or N-[2,6-dichloro-4-[(2-thienylsulfonyl) amino] benzoyl]-4-(2,6-dimethoxyphenyl)-L-phenylalanine, or the lower alkyl ester thereof such as the ethyl ester, or pharmacologically acceptable salts thereof.

(0038)

As the effective component of this invention, it is possible to use the ester or amide thereof. As ester, a) the lower alkyl ester which may be substituted by 1) pyridyl group, 2) amino group optionally substituted by lower alkyl group, 3) lower alkanoyloxy group, or 4) aryl group; b) lower alkenyl ester; c) lower alkinyl ester; d) lower cycloalkyl ester; and e) aryl ester are nominated. As amide may be nominated the amide ($-CONH_2$) which may be substituted by lower alkyl group, lower cycloalkyl group, aryl group, aryl lower alkyl group, hydroxy group or lower alkane sulphonyl group.

(0039)

Moreover, for ester of formula (I), for example, the ester is included which can be obtained by conversion in-vivo into the corresponding carboxylic acid, for example, lower alkyl ester, such as methyl ester and so on, lower alkanoyloxy ester such as acetoxymethyl ester or the like may be proposed. As the amide of formula (I), for example, N-unsubstituted amide, N-mono substituted amide such as N-lower alkyl amide or the like, N,N-disubstituted amide and the like such as N,N-(lower alkyl) (lower alkyl) amide or the like are included.

(0040)

The effective component of this invention, may be any of the free form or pharmacologically acceptable salt.

(0041)

As the pharmacologically acceptable salt of the compound of formula (I), for example salt of inorganic acid (hydrochloride, sulfate), salt of organic acid (p-toluenesulfonate, maleate), salt of inorganic base (salt of sodium salt or alkali metal such as for example potassium salt or the like) or salt of amine (ammonium salt)may be proposed.

(0042)

Further as pharmacologically acceptable salt, for example acid addition salt of inorganic acid or organic acid (for example nitrate, hydrobromide, methanesulfonate, acetate salt), or salt of inorganic base, organic base or amino acid (for example triethylamine salt, salt of lysine, salt of alkaline earth metal) may be proposed. Moreover, in pharmacologically acceptable salt, inner salt, adduct, solvate or hydrate is included.

(0043)

The effective component is formulated as a medicinal composition formed from the therapeutically effective amount of the aforesaid compound and the pharmacologically acceptable carrier.

(0044)

The composition of this invention can be used in the prevention or therapy of pathosis mediated by α 4 adhesion including α 4 β 1 and α 4 β 7 in a mammal such as a human and the like, in particular for α 4 β 7 adhesion mediated pathosis. This process comprises administering a therapeutically effective amount of the aforesaid compound or a composition to mammal or human patient.

(0045)

Medicinal composition of this invention is used for prevention or therapy of rheumatic arthritis, asthma, psoriasis, eczema, dermatitis such as contact dermatitis, atopic dermatitis or the like, diabetes mellitus, multiple sclerosis, systemic erythematosus (SLE), inflammatory enteric disease including ulcerative colitis and Crohn disease, graft versus host disease and disease conditions other than the aforesaid related to leukocyte invasion into gastrointestinal tract or skin, urethra, trachea, articulation synovial membrane and other epithelial tissue. Preferably, this composition is usable in prevention or therapy of inflammatory enteric disease such as ulcerative colitis and Crohn disease or the like.

(0046)

This invention relates to the following, namely, a method to inhibit the interaction between the cells having the ligand of MAdCAM-1 including α4 β7 integrin and MAdCAM-1 or a part thereof

(extracellular domain), by contacting the cells with the effective component of this invention. As one embodiment, this invention relates to the following, namely, a method to inhibit the MAdCAM-1 mediated interaction between the first cells having α4 β7 integrin and MAdCAM (for example, the second cells having MAdCAM), by contacting effective component of this invention with the first cells. In another embodiment, this invention relates to a therapeutic composition for an individual suffering from a disease accompanied by leukocyte recruitment to the tissue expressing MAdCAM-1 molecule (for example, endothelial cells).

(0047)

Another embodiment of this invention is related to a therapeutic composition for an individual suffering from a disease accompanied by leukocyte infiltration to tissue expressing MAdCAM-1 molecule.

(0048)

In accordance with this invention, cells having ligand of MAdCAM-1 are contacted with effective dose of effective component (one or more) represented by structural formula (I). The effective component is a compound that inhibits (decreases or prevents) the binding of ligand including MAdCAM-1 and α4 β7 integrin and/inhibits the induction of the ligand-mediated cells response. The therapeutically effective dose is an inhibitory quantity (for example, a sufficient quantity for inhibiting the adhesion of cells having MAdCAM-1 ligand and MAdCAM-1). The MAdCAM-1 ligand includes α4 β7 integrin such as human α4 β7 integrin and the like or homologues thereof from other species such as mouse or the like (hereinafter, called α4 βp of mouse or LPAM-1).

(0049)

For example, the adhesion of cells naturally expressing ligand of MAdCAM-1 such as leukocyte (for example, B lymphocyte, T lymphocyte) or the like or other cells expressing ligand of MAdCAM-1 (recombinant cells) to the MAdCAM-1 can be inhibited by the composition of this invention in vitro and/or in vivo.

(0050)

As another aspect, this invention relates to the following, namely, a therapeutic composition for an individual of a mammal such as human or other primate or the like suffering from a disease accompanied by leukocyte (for example lymphocyte, monocyte) infiltration (including recruitment and/or accumulation of leukocytes to the tissue) in tissue expressing MAdCAM-1 molecule. This composition is characterised in containing therapeutically effective dose of effective component of structural formula (I) (at least one or more kinds). For example, inflammatory diseases including disease accompanied by leukocyte infiltration to tissue expressing MAdCAM-1 molecule (for example endothelial cells) such as gastrointestinal tract including

stomach assembly endothelial cells, other mucosal tissue or venule of intrinsic layer of small intestine large intestine, mammary gland (lactation mammary gland) or the like can be treated by this composition. In the same way, an individual who has contracted a disease accompanying leukocyte infiltration in tissue as a result of binding of leukocyte to the cells expressing MAdCAM-1 molecule cells (for example endothelial cell) can be treated by the composition of this invention.

(0051)

As the diseases that can be treated in this way, there are ulcerative colitis, inflammatory bowel disease (IBD) such as Crohn disease or the like, pouchitis after proctocolectomy or post-ileoanostomy after IBD, and other gastrointestine disease accompanied by leukocyte infiltration for example celiac disease, nontropical sprue, serological reaction negative arthritis, and graft versus host disease or the like.

(0052)

Pancreatitis and insulin-dependent diabetes mellitus are other diseases that can be treated by the composition of this invention. The MAdCAM-1 is reported to be expressed in some blood vessels in paracrine pancreas of NOD (non-obesity diabetes mellitus) mouse in the same way as in BALB/c mouse and SJL mouse. The expression of MAdCAM-1 is induced on endothelium in inflammatory islet of pancreas of NOD mouse, and the MAdCAM-1 expressed on the NOD islet endothelium is an excellent indicator of an early stage of insulitis (Hanninnen A, et al., J. Clin. Invest. 92: 2509-2515 (1993)). Moreover, accumulation of lymphocyte expressing $\alpha 4\ \beta 7$ in pancreatic islet is observed, and MAdCAM-1 is participating in binding through $\alpha 4\ \beta 7$ of lymphoma cells to blood vessel of inflammatory islet (Haninnen A, et al., J. Clin. Invest. 92: 2509-2515 (1993)).

(0053)

As examples of inflammation diseases accompanied by the mucosa tissue which can be treated by this medicinal composition, mastitis (mammary gland), cholecystitis, cholangitis or pericholoangitis (bile duct and perihepatic tissue), chronic bronchitis, chronic sinusitis, asthma and graft versus host disease (in for example gastrointestinal tract) may be proposed. Moreover, chronic inflammatory disease of lung causing alveolar hypersensitivity, connective tissue disease (in SLE, rheumatoid arthritis), sarcoidosis and interstitial fibrosis such as other idiopathic diseases or the like, can be treated, too.

(0054)

The vascular cell adhesion molecule-1 (VCAM-1) recognizing $\alpha 4\ \beta 1$ integrin (VLA-4) is reported to play a role in leukocyte recruitment in vivo (Silver et al., J. Clin. Invest. 93; 1554-1563

(1994)). However, this therapeutic target seems to participate in more than one organic inflammatory processes. Unlike VCAM-1, the MAdCAM-1 is preferentially expressed in gastrointestinal tract and mucosa tissue, and it binds to α4 β7 integrin on leukocyte, and these cells are participating in homing on the mucosal site, for example, aggregated lymphoid nodule of gastrointestinal wall (Hamman et al., J. Immunol. 152: 3282-3293 (1994)). The inhibitor of binding of α4 β7 integrin with MAdCAM-1 has little effect on the other tissue types whose binding is mediated by other receptors, therefore a possibility of side effect is remote.

(0055)

The undesirable symptoms listed above can be relieved by administering this medicinal composition. The said symptoms are caused by the release of the pre-inflammatory mediators mediated by α4 β7 integrin as a result of unsuitable cell adhesion and/or cells activation. Such unsuitable cell adhesion or signal transduction is typically expected as a result of increased expression of VCAM and/or MAdCAM on endothelial cell surface. Increased expression of VCAM, MAdCAM and CS-1 will be due to normal inflammatory response or abnormal inflammatory condition.

(0056)

The suitable compound to use for therapy can be evaluated in vivo using suitable animal models. Suitable inflammatory animal models have been disclosed. For example, NOD mouse is an animal model of insulin-dependent diabetes mellitus. CD45 RBHi SCID model is a mouse model with similar to Crohn disease and ulcerative colitis (Powery, F, et al., Immunity, 1: 553-562 (1994)). Captive cotton top tamarins, a non-human primate species of the American Continent, often generate colitis spontaneously, which resembles human ulcerative colitis clinically and histologically (Madler, J.L, et, al, Gastroenterology, 88: 13-19 (1985)). Other animal models of gastroenteritis, tamarin model and BALB/c mouse (DSS (dextran sulfate sodium) induced inflammation model), and IL-10 knock out mice wherein gastrointestine lesion resembling lesion of human inflammation bowel disease have been disclosed (Strober, W. and Arnhalt, R.O, Cell, 75: 203-205 (1993)).

(0057)

In accordance with this invention, effective component can be administered alone or with other pharmacologically active agents (sulfasalazine, antiinflammatory compound, steroid or other nonsteroidal antiinflammatory compound) to an individual. The compound may be administered before, at the same time as, or after the administration of other pharmaceutical agents, in sufficient quantity to reduce or prevent MAdCAM-mediated binding of MAdCAM-1 ligand such as for example human α4 β7 or the like.

(0058)

Effective dose of effective component can be administered by single dosing or multiple dosing by a suitable route. The effective dose is a sufficient amount to achieve the desired therapeutic effect and/or preventive effect, for example, a sufficient amount for reducing or inhibiting MAdCAM mediated binding to MAdCAM-1 ligand, and thereby suppressing leukocyte adhesion and invasion, and accompanying cellular responses. The suitable quantity of effective component of this invention for therapy, prevention or diagnosis can be determined using already known process in this field, for example, it is determined by age, sensitivity, resistance and overall conditions of the individual.

(0059)

The effective component of this invention or pharmacologically acceptable salts thereof can be administered non-orally or orally, as suitable medicinal composition, for example, it can be, in accordance with conventional procedures, used as tablet, granule, encapsulated formulation, powdered drug, injection and inhalant.

(0060)

The dose of effective component of this invention or a pharmacologically acceptable salt thereof varies depending on administration pathway, age of patient, body weight, a condition, but however in general daily dose is preferably range of about 0.1-100 mg/kg, in particular preferably 1-100 mg/kg.

(0061)

As described above, the effective component of formula (I) can be formulated as medicinal composition. When deciding the compound of formula (I), according to circumstance, for the treatment of disease presented, the disease itself and its degree of severity, and the age, sex, body weight and symptoms of the patient are also things to be considered to determine the therapy of given disease.

(0062)

During medical use, dose of the compound of formula (I) needed in order to achieve therapy effect will of course be varied according to the individual compound, administration pathway, treated therapy person and pathosis or disease of treated individual. The dose per day of compound of formula (I) or a pharmacologically acceptable salt thereof is calculated for a mammal thought to have contracted any of the aforesaid diseases or thought possibly to have contracted any of the aforesaid diseases, and is between 0.1 mg-100 mg per 1 kg in weight of whole body of a said mammal and, in case of systemic administration, is 0.5-100 mg / kg of mammal body weight, and is most preferably between 0.5-50 mg / kg and it is divided into two or

three times per day and administered. In case of local application, when it is administered to for example skin and eye, suitable dose is 0.1 μ g-100 μ g per 1 kg, typical about 0.1 μ g / kg.

(0063)

In case of oral administration, the dose of the compound of formula (I) or a pharmacologically acceptable salt thereof is preferably between 1mg-50mg per 1 kg and most preferably 5 mg-25 mg per mammal 1 kg in weight, for example 1-10 mg. Most preferably unit dose of medicinal composition for oral administration in range of this invention contains about 1.0 g or less of the compound of formula (I) .

(0064)

As for the medicinal composition of this invention, here, the patient with a pathosis as abovementioned can be administered a quantity which has the effect of partly or completely partially relieving the undesired symptom. Symptoms are thought to be generated by release of preinflammatory mediators mediated by α 4 β 7 integrin due to unsuitable cell adhesion and cell activation. Such unsuitable cell adhesion or signal transduction is expected as a result of increased expression of VCAM-1 and/or MAdCAM on endothelial cell surface typically. Expression increase of VCAM-1, MAdCAM and CS-1 will be due to the normal inflammation response or abnormal inflammation condition. In either case, effective dose of the compound of this invention decreases cell adhesion increase due to the expression increase of VCAM-1 and MAdCAM by endothelial cell. 50 % reduction of adhesion observed in pathosis is regarded as effective decrease of adhesion. More preferably adhesion is reduced by 90 % in ex vivo. Most preferably adhesion mediated by the mutual interaction of VCAM-1, MAdCAM and CS-1 is checked by effective dose completely. Clinically, in some cases, effect of the compound is observed as decrease of white blood cells invasion to tissue or lesion site. Thereafter, in order to relieve the symptom that is not desirable, the quantity of a composition of this invention is administered that is effective in order to reduce or eliminate unsuitable cell adhesion or unsuitable cell activation in order to obtain therapy effect.

(0065)

Effective component can be administered alone, but it is preferred to be used as medicinal composition including the compound of formula (I) and pharmacologically permitted carrier. Such preparation is a further characteristic of this invention.

(0066)

The preparation of this invention for the human and veterinary medical applications, comprises the compound of formula (I) and pharmacologically permitted carrier and at times, the other therapeutically effective component which is generally known as effective in disease or therapy

of pathosis of the subject. Carrier must be the one which does not react with other component of preparation and is not harmful to recipient.

(0067)

As preparation, a preparation is nominated which is suitable for oral, pulmonary, ophthalmic, rectal, perenteral (subdermal, intramuscular and intravenous are included), intraarticular, local, transnasal inhalant (with aerosol) or buccal administration. The already known maintenance preparation is included in the field of this to such preparation. Oral and parenteral administration routes is preferred administration system.

(0068)

Unit administration form of the preparation is suitable, and preparation can be prepared by process which is well known in the pharmaceutical field. The whole process includes step to mix effective component with the carrier which is one or more supplement component. Generally the preparation is prepared by mixing the effective component uniformly and completely with a liquid support or finely powdered solid support or both, and thereafter, forming the product in desired form in accordance with requirements.

(0069)

The preparation of this invention suitable for oral administration, in the form of a unit dose which was respectively separated such as for example encapsulated formulation, cachet, tablet, lozenge and so on, and each unit dose contains the effective component of quantity determined beforehand, in the form of powder, granule or aqueous liquid solution or suspension. Other used preparation includes non-aqueous liquid, oil-in-water emulsion, water-in-oil emulsion, aerosol, cream agent or ointment, or in the form of impregnant to a percutaneous patch agent for administration of the effective component percutaneously, for administration to the patient as required. The effective component of composition of this invention can also be administered to the patient in the form of a bolus agent, electuary or paste, as required.

(0070)

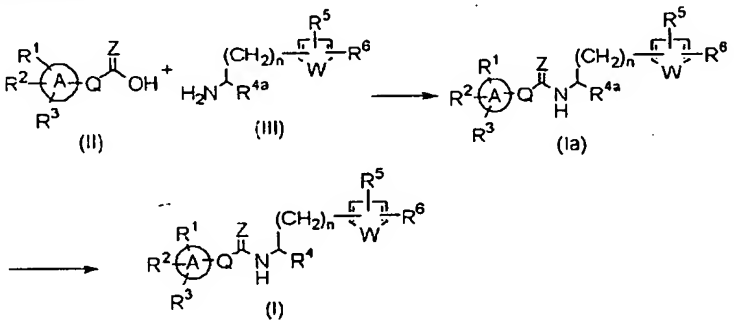
As drug carrier suitable to oral administration, for example, binding agent (syrup, gum arabic, gelatin, sorbitol, tragaganth, polyvinylpyrrolidone and the like), excipient (lactose, sugar, corn starch, potassium phosphate, sorbitol, glycine and the like), lubricant (magnesium stearate, talc, polyethyleneglycol, silica and the like), disintegrating agent (potato starch and the like) or wetting agent (sodium lauryl sulfate and the like) may be proposed. On the other hand, when it is administered parenterally, it is an injection agent or drip infusion agent using for example distilled water for injection, physiological saline, dextrose aqueous solution injection, and so on or it is possible to form suppositories.

(0071)

"Leminton: chemistry and practice of pharmacology", 19th revised edition, c.1995 by Philadelphia pharmaceutical chemistry university can be referred to as a commentary book of medicinal composition. In accordance with this invention, the compound (I) can be prepared using the following method.

(0072)

Production method A.



(wherein R4a is ester group and the other symbols are the same as above).

(0073)

The compound of formula (I) or a pharmacologically acceptable salt thereof is prepared as follows.

(1). The compound of formula (II), salts thereof or reactive derivative thereof is condensed with compound or salts thereof of formula (III). (2). In accordance with requirements ester group of the compound of formula (Ia) is converted into carboxyl group. (3) In accordance with requirements carboxyl group of the obtained compound is transformed further into ester group, amide group, tetrazolyl group or a pharmacologically acceptable salt thereof. For example, salt of compound (II) and/or (III), salt of inorganic acid such as for example trifluoroacetic acid salt, hydrochloride, sulfate or the like, alkali metal salt such as for example sodium salt and potassium salt or the like, salt of inorganic base such as for example alkaline earth metal salt or the like such as for example barium salt and calcium salt or the like may be proposed.

(0074)

(1). Condensation reaction can be carried out by general process for ordinary amide bond synthesis. The condensation reaction of compound (II) or salt thereof with compound (III) or salt thereof, is carried out in the absence or in the presence of base (organic base such as for example DIEA, DMAP, DBU, Et_3N, alkali metal hydride, alkali metal carbonate, alkali metal hydrogen carbonate) it is carried out in the presence of condensing agent (for example BOP-Cl,

BOP reagent, DCC, EDC or CDI) in absence of solvent or in the presence of a suitable solvent (for example methylene chloride, THF, DMF or a mixed solvent thereof).

(0075)

Reaction is performed at 0°C to room temperature (preferably room temperature).

(0076)

Condensation reaction the compound (III) or salts thereof and reactive derivative of the compound (II) (for example acid halide, reactive ester, mixed acid anhydride with another carboxylic acid) is performed in the absence of solvent or the presence of a suitable solvent (CH2Cl2, diethyl ether, THF, DMF, toluene, or a mixed solvent thereof) in the absence or in the presence of base (organic base such as for example DIEA, DMAP, DBU, Et_3N, alkali metal hydride, alkali carbonate metal, alkali metal bicarbonate) .

(0077)

Reaction is performed between from -30 to 100°C.

(0078)

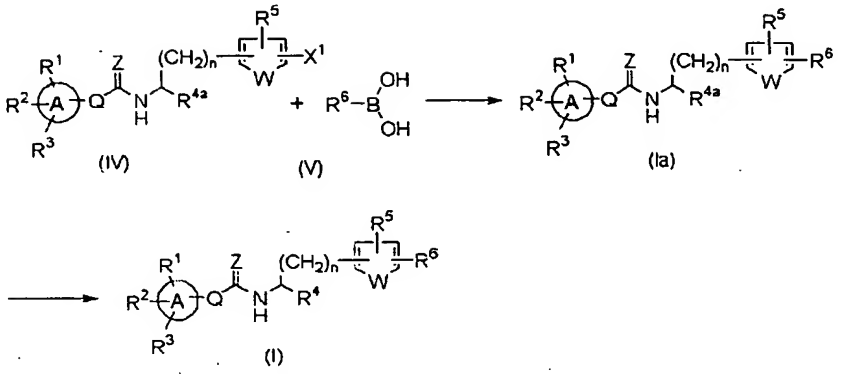
(2). Conversion from ester group to carboxyl group is performed by conventional method selected according to the kind of converted ester group. For example, hydrolysis using base such as LiOH, NaOH or acid such as HCl; acid treatment such as TFA and so on; catalytic reduction used catalyst such as palladium carbon or the like; may be proposed. Ester group is selected from the ordinary ester, for example, lower alkyl ester, lower alkenyl ester, lower alkynyl ester, aryl lower alkyl ester (for example benzyl ester), aryl ester (for example phenyl ester) and the like may be proposed.

(0079)

(3). Conversion from carboxylic acid to ester group, amide group or tetrazolyl group, or conversion of the compound to pharmacologically acceptable salt thereof is performed in accordance with conventional procedures. In particular, conversion is performed in the same way as in process of production method A-(1) to ester group or amide group from carboxyl group. Conversion to tetrazolyl group from carboxyl group is described with later described step N.

(0080)

Production method B.



(wherein. X1 is leaving group and the other symbols are the same as above).

(0081)

The compound of formula (I) is synthesised as follows.

(1). The compound of formula (IV) is reacted with the compound of formula (V).

(2). In accordance with requirements ester group of the compound of formula (Ia) is converted into carboxyl group.

(3). In accordance with requirements carboxyl group of the obtained compound is transformed into ester group, amide group, tetrazolyl group or a pharmacologically acceptable salt thereof furthermore. As leaving group of X1, halogen atom, trifluoromethane sulfonyl oxy group may be proposed.

(0082)

(1). Coupling reaction is performed using ordinary aryl coupling process. For example Suzuki coupling process (reference of Suzuki coupling process, (a) Suzuki et al. Synth. Commun. 1981, 11, 513, (b) Suzuki, Pure and Appl, Chem. 1985, 57, 1749-1758, (c) Suzuki et al., Chem. Rev. 1995, 95, 2457-2483, (d) Shay et al., J. Org, Chem. 1992, 57, 379-381, (e) Martin et al., Acta Chemica Scandinavica, 1993, 47, 221-230).

(0083)

The coupling reaction is performed for example between from room temperature to 100°C, preferably between from 80°C to 100°C in the presence of tetrakis (triphenylphosphine) palladium and base (inorganic base such as for example potassium carbonate and the like) in organic solvent. An organic solvent which does not hinder coupling reaction is OK, for example toluene, DME, DMF, water or a mixed solvent thereof may be proposed.

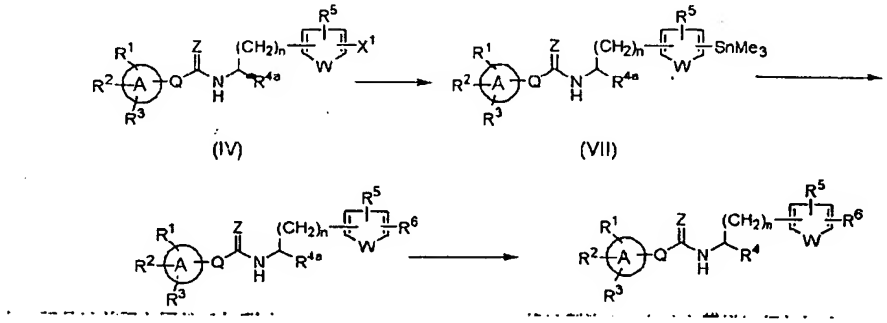
(0084)

(2). Conversion is performed in the same way as in production method A-(2) from ester group to carboxyl group.

(3). The conversion or the compound is transformed into pharmacologically acceptable salt thereof, and it is performed in the same way as in production method A-(3) from carboxyl group to ester group, amide group or tetrazolyl group.

(0085)

Production method C.



(wherein, the symbols have the same said definitions).

(0086)

Also the compound of formula (I) is synthesised as follows.

(1). The compound (IV) is converted into corresponding organotin compound (for example the compound of formula (VII)) .

(2). The compound (VII) is reacted with the compound of formula (VIII)

R6-X (VIII)

(wherein, X is leaving group and R6 is the same as above) .

(3). In accordance with requirements ester group of the compound of formula (Ia) is converted into carboxyl group, and

(4). In accordance with requirements carboxyl group of the obtained compound is transformed into ester group, amide group, tetrazolyl group or a pharmacologically acceptable salt thereof furthermore. As leaving group X, halogen atom, trifluoromethane sulfonyl oxy group may be proposed.

(0087)

(1). It is possible to carry out conversion to organotin compound (VII) from the compound (IV) for example, the compound (IV) with hexaalkyl di tin (for example hexamethyl di tin) in organic solvent (for example dioxane, toluene, DME, DMF, water or a mixed solvent thereof) in the presence of tetrakis (triphenylphosphine) palladium and addition agent (for example LiCl) between from 150°C (110°C) and room temperature.

(0088)

(2). Coupling reaction is performed using ordinary aryl coupling process, for example Stille coupling process (Stille coupling process reference = Stille et al., Angew, Chem. Int, Ed. Engl, 25, 508(1986)) . Coupling reaction is performed in organic solvent (for example toluene, DME, DMF, water or a mixed solvent thereof) in the presence of tetrakis (triphenylphosphine) palladium at for example from room temperature to150°C (preferably, at from 80°C to 120°C).

(0089)

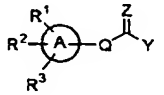
(3). Conversion is performed in the same way as in production method A-(2) from ester group to carboxyl group.

(0090)

(4). The conversion is performed in the same way as in production method A-(3) from carboxyl group to ester group or amide or tetrazolyl group, or the compound is transformed into pharmacologically acceptable salt thereof.

(0091)

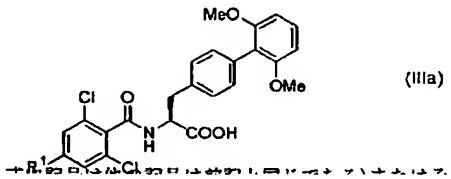
The compound (IV) can be synthesised by reacting a compound of formula (IIa)



(IIa)

(wherein Y is a halogen atom, and the other symbols are the same as above) with a compound of formula (IIIa)

(0092)



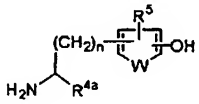
(IIIa)

(wherein the symbols are the same as above) or a salt thereof by ordinary peptide synthesis process and the condensation reaction of the aforesaid compound (III) or salts thereof and reactive derivative of the compound (II) (for example acid halide), is performed similarly.

(0093)

Also the compound (IV) can be synthesized such as following.

(1). Compound (IIa) is condensed with the compound of formula (IIIb) or salts thereof



(IIIb)

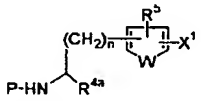
(the symbol are the same as above) in the same way as above-mentioned.

(2). Hydroxy group of the obtained compound is converted into leaving group in accordance with conventional procedures. For example, conversion from hydroxy group can be carried out in organic solvent (for example CH2Cl2, THF or a mixed solvent thereof) in the presence of base (for example pyridine, NEt3, DIEA) using anhydrous trifluoromethanesulfonic acid at 0°C to trifluoromethane sulfonyl oxy group.

(0094)

The compound (II) can be synthesized such as following.

(1). The compound of formula (VIa)



(VIa)

(wherein, P, is the protecting group of amino group, and the other symbols are same as above) and the compound (V) are condensed using ordinary aryl coupling process known as Suzuki coupling process.

(2). Protecting group of amino group of the obtained compound is eliminated.

(0095)

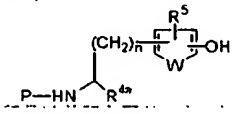
Protecting group of amino group is selected from the protecting group of ordinary amino group, for example substituted or unsubstituted aryl lower alkoxycarbonyl group (for example benzyloxycarbonyl group, p-nitrobenzyl oxycarbonyl group), lower alkoxycarbonyl group (for example t-butoxycarbonyl group) and the like may be proposed.

(0096)

The elimination of protecting groups of amino group is performed in accordance with conventional procedures, and that removal process should be selected depending on the kind of protecting group that is removed, for example, catalytic reduction using catalyst (for example palladium carbon), acid (for example TFA) treatment may be proposed. Condensation reaction is performed in the same way as in coupling reaction of compound (IV) and (V).

(0097)

The compound (VIa) wherein X1 is trifluoromethane sulfonyl oxy group X1 can be synthesised from the compound of formula (VIb)



(VIb)

(the symbol are the same as above) and anhydrous trifluoromethanesulfonic acid in the same way as in synthesis of the compound (IV).

(0098)

The compound (V) can be synthesized in accordance with conventional procedures (cf. (a) Quivira et al., J. Am. Chem. Soc. 1961,83,2159, (b) Gerald, The Chemistry of Boron, Academic Press= New York, 1961,(c) Muetterties, The Chemistry of Boron and its Compounds, Wiley= New York, 1967,(d)Allamanza et al., J. Am. Chem, Soc. 1994,116,11723-11736) =.

(0099)

(1). Substituted or unsubstituted aryllithium or substituted or unsubstituted heteroaryl lithium is reacted in organic solvent (for example diethyl ether, THF or a mixed solvent thereof) at between from-100°C to room temperature with trimethyl borate.

(2). The obtained compound is hydrolysed in accordance with conventional procedures. Hydrolysis is performed at room temperature in the presence of mild acid (for example AcOH or citric acid) in organic solvent (for example diethyl ether, THF or a mixed solvent thereof). The target compounds of this invention (I) can be interconverted. Conversion is performed by selecting one of following step (step A-W) by kind of substituent in organic solvent to other compound of this invention (I) from the compound of this invention (I). Organic solvent selects the one which does not hinder said step.

(0100)

Step A

Reduction of carbonyl group.

The compound (I) wherein substituent of R1, R2, R3, R5 or R6 is hydroxy lower alkyl group such as hydroxymethyl or the like or lower alkyl-CH(OH)-group is obtained by reducing the compound (I) wherein corresponding substituent R1, R2, R3, R5 or R6 is carboxyl group, formyl group or lower alkyl-CO-. Reductive reaction is performed in accordance with conventional procedures, using a reducing agent such as for example borane, alkali metal borohydride (for example sodium borohydride) at 0°C-room temperature in organic solvent (methanol, ethanol, THF or a mixed solvent thereof) .

(0101)

Step B

Oxidation of formyl group.

The compound (I) wherein substituent of R1, R2, R3, R5 or R6 is carboxyl group is obtained by oxidising the compound (I) wherein corresponding substituent R1, R2, R3, R5 or R6 is formyl group. Oxidation reaction is performed in accordance with conventional procedures using oxidant such as KMnO4 or the like, at 0°C-50°C (preferably 30°C-50°C), it in organic solvent such as acetone or the like, water or a mixed solvent thereof.

(0102)

Step C

Reduction of nitro group.

The compound (I)wherein the substituent R1, R2, R3, R5 or R6 is amino group or has amino group is obtained by reducing the substituent of corresponding R1, R2, R3, R5 or R6 of the compound (I) which is nitro group or has the nitro group. Reductive reaction is performed in accordance with conventional procedures. 1). Catalytic reduction using reducing agent such as Raney nickel and palladium carbon or the like, in organic solvent such as methanol or the like, water or a mixed solvent thereof at room temperature under a hydrogen atmosphere, 2). Chemical reduction using metal and inorganic acid (for example Fe / HCl, Sn / HCl or the like). or 3). Reduction in the absence or the presence of suitable solvent such as methanol, ethanol, water or the like or mixed solvent thereof, using reducing agent such as Na2S2O4 or the like by temperature of 0-80°C.

(0103)

Step D

Elimination of protecting group.

(D-1)

The compound (I) wherein the substituent of R1, R2, R3, R5 or R6 is amino group or to have amino group is obtained by deprotecting the compound (I) wherein the amino group of the substituent of corresponding R1, R2, R3, R5 or R6 has N-protected amino group or is a group which has N-protected amino group, wherein the protecting group is ordinary protecting group of amino group (for example benzyloxycarbonyl group, tert butoxycarbonyl group, 9-fluorenylmethoxycarbonyl group or the like). Deprotecting reaction is performed using conventional method selected by kind of protecting group eliminated, for example, 1). The catalytic reduction that was used under hydrogen palladium carbon, 2). Acid treatment such as

hydrochloric acid or TFA. 3). Amine treatment such as piperidine or the like, 4). Catalyst treatment such as Wilkinson catalyst or the like, is possible to carry out with absence of solvent or in organic solvent such as in CH2Cl2, THF, methanol, ethanol, acetonitrile or the like under heat or at room temperature.

(0104)

(D-2)

Substituent of corresponding R1, R2, R3, R5 or R6 is N-protection sulphamoyl group, and the compound (I) wherein substituent of R1, R2, R3, R5 or R6 is sulphamoyl group is obtained by deprotecting compound (I) wherein the protecting group is ordinary protecting group of sulphamoyl group, for example tert-butyl group. Deprotecting reaction is performed using conventional method selected by kind of eliminated protecting group, for example it can be performed with acid such as TFA, at room temperature, in organic solvent such as CH2Cl2 or the like, or in the absence of solvent.

(0105)

(D-3)

The compound (I) wherein substituent of R1, R2, R3, R4, R5 or R6 is carboxyl group or has carboxyl group is obtained by deprotecting compound (I) wherein substituent of corresponding R1, R2, R3, R4, R5 or R6 is protected carboxyl group or has protected carboxyl group, and the protecting group is ordinary protecting group of carboxyl group (for example lower alkyl group, aryl lower alkyl group or the like). The deprotecting reaction was selected by kind of protecting group eliminated, for example, the hydrolysis which was performed in accordance with conventional procedures, and was using base such as for example NaOH, LiOH, KOH or acid such as hydrochloric acid or the like, treatment with acid such as for example TFA or the like, catalytic reduction using catalyst such as palladium carbon or the like using at room temperature in organic solvent such as methanol, ethanol, or THF or under absence of solvent, can be performed.

(0106)

(D-4)

The compound (I) substituent of R1, R2, R3, R5 or R6 is hydroxy group or to have hydroxy group is obtained by deprotecting compound (I) wherein the substituent of corresponding R1, R2, R3, R5 or R6 is protected hydroxy group or has protected hydroxy group, and the protecting group is ordinary protecting group of hydroxy group (for example methyl group, methoxy methyl group, tetrahydropyranyl group or the like). Deprotecting reaction is performed by conventional method selected by kind of eliminated protecting group, for example demethylation of methoxy group by treatment using BBr3 and removal of methoxy methyl group by

hydrochloric acid in organic solvent such as CH2Cl2 and methanol or the like at from room temperature to 78°C, can be carried out.

(0107)

Step E

Acylation of amino group.

(E-1)

The compound (I) wherein the substituent of R1, R2, R3, R5 or R6, is N-acylamino-group for example lower alkanoyl amino group, lower alkoxycarbonylamino group, aryl carbonylamino group, chloro sulfonyl carbamoyl amino group such as 3-chloro sulfonyl ureide group or the like, lower alkyl carbamoyl amino group such as 3-lower alkyl ureide group or the like, substituted or unsubstituted aryl carbamoyl amino group such as 3-(substituted or unsubstituted aryl) ureido group or the like, substituted or unsubstituted lower alkyl thiocarbamoyl amino group such as 3-lower alkyl thioureido group, 3-phenyl lower alkyl thiouredide group or the like is obtained from the corresponding compound (I) wherein the substituent R1, R2, R3, R5 or R6 is amino group by performing N-acylation reaction in accordance with conventional procedures. The N-acylation reaction is performed according to conventional procedures using 1). acylating agent such as lower alkanoyl halide, lower alkanoic acid anhydride, lower alkyl halo formate, aryl carbonyl halide, chloro sulfonyl isocyanate, lower alkyl isocyanate, substituted or unsubstituted aryl isocyanate or lower alkyl isocyanate or the like, or, 2). when synthesising lower alkoxycarbonylamino group, lower alkyl carbamoyl amino group, substituted or unsubstituted aryl carbamoyl amino group, substituted or unsubstituted lower alkylthiocarbamoyl amino group, using condensing agent such as CDI, thio CDI and necessary amine or alcohol, between 0°C-100°C (90°C) in the presence of base such as DIEA, pyridine, sodium bicarbonate, potassium carbonate or the like, or in their absence, in organic solvent such as THF, acetonitrile, CH2Cl2, DMF, toluene or the like or mixed solvent thereof.

(0108)

(E-2)

Compound (I) wherein substituent of R1, R2, R3, R5 or R6 is N-lower alkyl sulfonyl amino group, such as methanesulphonyl amino group or the like, N-substituted or unsubstituted arylsulfonylamino group or the like such as p-toluenesulfonyl amino group, benzensulphonyl amino group or the like or N-substituted or unsubstituted heteroaryl sulfonyl amino group such as quinolinosulfonylamino group is obtained from the compound (I) wherein substituent of corresponding R1, R2, R3, R5 or R6 is amino group by N-sulphonylating. The N-sulphonylation reaction is performed in accordance with conventional procedures in organic solvent such as CH2Cl2, THF, DMF, acetonitrile, toluene or the like or mixed solvent thereof at between from

0°C to room temperature (at preferably room temperature) in the presence of base such as pyridine, Et_3N, DIEA, sodium bicarbonate, potassium carbonate or the like with lower alkyl sulfonyl halide, substituted or unsubstituted aryl sulfonyl halide or substituted or unsubstituted heteroaryl sulfonyl halide.

(0109)

(E-3)

The compound (I) wherein substituent of R1, R2, R3, R5 or R6 is ureido group is obtained by hydrolysing the compound (I) wherein corresponding substituent R1, R2, R3, R5 or R6 is 3-chloro sulfonyl ureido group. Hydrolysis can be performed using base such as for example LiOH, NaOH or the like or acid such as HCl at room temperature in a suitable solvent such as THF, CH3CN, DMF, water or the like or mixed solvent thereof.

(0110)

Step F

Alkylation of hydroxy group

Compound (I) wherein substituent of R1, R2, R3, R5 or R6, is substituted or unsubstituted lower alkoxy group such as for example substituted or unsubstituted hetero cycloalkyl lower alkoxy group (for example, substituted or unsubstituted piperidyl lower alkoxy group, substituted or unsubstituted pyrrolidinyl lower alkoxy group), aryl lower alkoxy group, heteroaryl lower alkoxy group (for example pyridyl lower alkoxy group, substituted or unsubstituted thiazolyl substituted alkoxy group, substituted or unsubstituted isoxazolyl lower alkoxy group, substituted or unsubstituted thienyl lower alkoxy group), lower alkoxycarbonyl lower alkoxy group, carboxy lower alkoxy group, hydroxy lower alkoxy group, cyano lower alkoxy group or lower alkoxy group or the like is obtained by alkylating the compound (I) wherein corresponding substituent R1, R2, R3, R5 or R6 is hydroxy group, and thereafter, in accordance with requirements deprotecting the protecting group of carboxyl group or hydroxy group in accordance with conventional procedures. Alkylation reaction, is performed in accordance with conventional procedures using unsubstituted halogenated lower alkane (for example iodomethane) or substituted halogenated lower alkane such as substituted or unsubstituted aryl group (for example unsubstituted aryl lower alkyl halide such as benzyl bromide or the like), substituted or unsubstituted heteroaryl group (for example substituted or unsubstituted heteroaryl lower alkyl halide such as pyridylmethyl bromide, isoxazolyl methyl bromide, thiazolyl methyl bromide or the like), hetero cycloalkyl group (for example substituted hetero cycloalkyl lower alkyl halide such as N-lower alkyl pyrrolidinyl lower alkyl bromide, N-lower alkyl piperidyl lower alkyl bromide or the like), lower alkoxycarbonyl group (haloalkane acid lower alkyl ester such as for example methyl bromoacetate or the like), or cyano group (for example bromo acetonitrile), in organic solvent such as CH2Cl2, THF, DMF, acetonitrile, toluene or the like at between from

room temperature to 50°C in the presence of a base such as for example Et_3N, DIEA, sodium bicarbonate, potassium carbonate and the like.

(0111)

Alkylation reaction is performed using ordinary alkylation method such as Mitsunobu reaction or the like (reference of Mitsunobu reaction, (a) Mitsunobu = Synthesis, 1-2 8, (1981), (b) Huw, Organic Reactions, 42,335 (1992), Mitsuhashi et al., J. Am. Chem, Soc, 94, 26 (1972)).

(0112)

Step G

Halogenation of hydroxy group

The compound (I) wherein substituent of R1, R2, R3, R5 or R6 is halogenated lower alkyl group is obtained by halogenating the compound (I) wherein corresponding substituent R1, R2, R3, R5 or R6 is hydroxy lower alkyl group. For example, halogenation can be carried out by conventional method using combination of triphenylphosphine and tetrahalomethane such as CBr4 or the like, at room temperature in organic solvent such as CH2Cl2 or the like.

(0113)

Step H

Conversion of alkyl halide group to alkoxyalkyl group

The compound (I) wherein substituent of R1, R2, R3, R5 or R6 is lower alkoxy lower alkyl group is obtained by reacting compound (I) wherein corresponding substituent R1, R2, R3, R5 or R6 is halogenated lower alkyl group in organic solvent such as DMF, THF, acetonitrile or the like with alkali metal lower alkoxide such as sodium methoxide or the like at room temperature.

(0114)

Step I

Conversion to carbamoyl group of carboxyl group.

The compound (I) wherein substituent of R1, R2, R3, R4, R5 or R6 is substituted or unsubstituted carbamoyl group such as N-lower alkyl carbamoyl group, N,N-(lower alkyl) (lower alkyl) carbamoyl group, N-(hydroxy lower alkyl) carbamoyl group, N-(morpholino lower alkyl) carbamoyl group, N-(aryl lower alkyl) carbamoyl group, N-lower alkane sulfonyl carbamoyl group, hydroxy carbamoyl group, carbamoyl group or the like, is obtained from the compound (I) wherein corresponding substituent R1, R2, R3, R4, R5 or R6 is carboxyl group, by condensing with substituted or unsubstituted amine (for example lower alkyl amine, N,N-(lower alkyl) (lower alkyl) amine, (hydroxy lower alkyl) amine, (morpholino lower alkyl) amine, (aryl lower alkyl) amine, hydroxyamine, ammonia) or lower alkane sulfonamide. Condensation reaction can be

carried out by ordinary peptide synthesis reaction in the same way as in condensation reaction of the said compound (II) and (III).

(0115)

Step J

Reductive alkylation.

(J-1)

The compound (I) wherein substituent of R1, R2, R3, R5 or R6 is amino lower alkyl group, lower alkyl amino lower alkyl group or arylamino lower alkyl group, is obtained by reductive alkylation of compound (I) wherein corresponding substituent R1, R2, R3, R5 or R6 is formyl group, using ammonia, lower alkyl amine or arylamine. Reductive alkylation reaction can be carried out by conventional method, with reducing agent such as sodium cyanoborohydride or the like and acid such as hydrochloric acid or the like at room temperature in organic solvent such as methanol, THF, dioxane or mixed solvent thereof or the like.

(0116)

(J-2)

The compound (I) wherein substituent of R1, R2, R3, R5 or R6 is N,N-dimethylamino group is obtained by reductive alkylation of compound (I) wherein corresponding substituent R1, R2, R3, R5 or R6 is amino group. Reductive alkylation reaction is carried out by conventional method using reducing agent such as sodium cyanoborohydride, formaldehyde, or the like and acid such as hydrochloric acid or the like at room temperature in organic solvent such as dioxane methanol, ethanol, THF or the like or water or a mixed solvent thereof.

(0117)

Step K

Wittig reaction.

The compound (I) wherein substituent of R1, R2, R3, R5 or R6 is lower alkoxycarbonyl ethenyl group is obtained from the compound (I) wherein corresponding substituent R1, R2, R3, R5 or R6 is formyl group using Wittig reaction. For example, Wittig reaction can be carried out by conventional method in organic solvent such as toluene, THF at temperature of 50-100°C using triphenylphosphoranylidene acetic acid lower alkyl ester.

(0118)

Step L

Conversion to amino alkyl group of alkyl halide group

The compound (I) wherein substituent of R1, R2, R3, R5 or R6 is lower alkyl group substituted by substituted or unsubstituted pyrrolidinyl group, substituted or unsubstituted amino group,

substituted or unsubstituted piperidinyl group, substituted or unsubstituted morpholino group, optionally oxidised thiomorpholino group or substituted or unsubstituted piperazinyl group can be by carrying out (sic) the reaction of a compound (I) wherein corresponding substituent R1, R2, R3, R5 or R6 is halogenated lower alkyl group with necessary amine in the absence or in the presence of base such as Et_3N, DIEA in the absence of solvent or in the presence of organic solvent such as DMF, THF, CH2Cl2 or the like at room temperature or while cooling. More particularly, the compound (I) wherein R1 and R5 are hydrogen atoms, and R2 and R3 are halogen atoms, and R6 is phenyl group substituted by lower alkoxy group and lower alkyl group substituted by group selected from substituted or unsubstituted amino group, substituted or unsubstituted piperidinyl group, substituted or unsubstituted morpholino group, substituted or unsubstituted piperazinyl group and substituted or unsubstituted pyrrolidinyl group is obtained by the reaction of a compound (1) wherein R1 and R5 are hydrogen atoms, R2 and R3 are halogen atoms and R6 is phenyl group substituted by lower alkoxy group and halogenated lower alkyl group with necessary amine such as substituted or unsubstituted ammonia, substituted or unsubstituted piperidine, substituted or unsubstituted morpholine, substituted or unsubstituted piperazine or substituted or unsubstituted pyrrolidine or the like. The reaction can be carried out as above.

(0119)

Step M

Conversion to thiocarbonyl group of carbonyl group

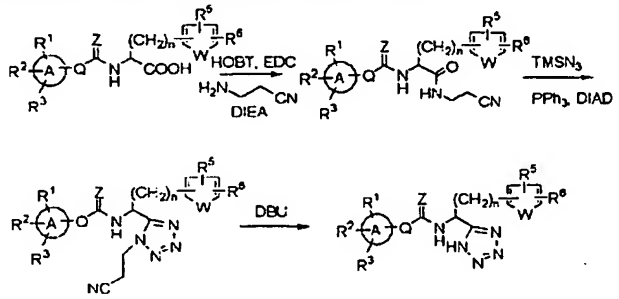
The compound (I) wherein Z is sulfur atom is obtained by reacting the compound (I) wherein Z is oxygen atom at between from 50 to 150°C in suitable organic solvent such as toluene, xylene or the like with Lawsone reagent.

(0120)

Step N

Conversion to tetrazolyl group of carboxyl group

The compound (I) wherein R4 is tetrazolyl group is obtained using the compound (I) wherein R4 is carboxyl group using process in accordance with J. Med. Chem. 41, 1513-1518, 1998. An outline of these step is shown in the following reaction equation.



(0121)

Step O

Conversion from carboxyl group to alkoxycarbonyl group

The compound (I) wherein substituent of R1, R2, R3, R4, R5 or R6 is substituted or unsubstituted lower alkoxycarbonyl group is obtained by condensing the compound (I) wherein corresponding substituent R1, R2, R3, R4, R5 or R6 is carboxyl group, with substituted or unsubstituted lower alcohol such as halo lower alcohol, pyridyl lower alcohol, lower alkyl amino lower alcohol, lower alkoxy lower alcohol or the like. Condensation reaction can be carried out by conventional method of ordinary ester synthesis same as in the said production method A-(3) .

(0122)

Step P

Reduction of hydroxy group

The compound (I) wherein substituent of R1, R2, R3, R5 or R6 is lower alkyl group is obtained by reducing the compound (I) wherein corresponding substituent R1, R2, R3, R5 or R6 is hydroxy-lower alkyl group. Reductive reaction is carried out by using reducing agent such as for example silane compound (for example Et3SiH) at temperature between 0°C and 78°C in suitable organic solvent such as acetonitrile, CH2Cl2, THF in the presence of Lewis acid such as BF3, TiCl4 or the like.

(0123)

Step Q

Halogenation of phenyl group

The compound (I) wherein R6 is substituted or unsubstituted halophenyl group is obtained by reacting the compound (I) wherein corresponding R6 is substituted or unsubstituted phenyl group while heating or at room temperature with halogenating agent such as Bu_4NBr_3 ,3,5-dichloro-1-fluoro pyridinium triflate or the like in suitable solvent such as CH_2Cl_2, THF, acetonitrile or the like.

(0124)

Step R

Nitration reaction of phenyl group

The compound (I) wherein R6 is substituted or unsubstituted nitrophenyl group can be obtained by reacting the compound (I) wherein corresponding R6 is substituted or unsubstituted phenyl group with nitric acid at temperature of from room temperature to 100°C in suitable solvent such as acetonitrile, THF, methanol, ethanol or the like.

(0125)

Step S

Conversion of phenyl group to carbamoyl phenyl group

The compound (I) wherein R6 is substituted or unsubstituted carbamoyl phenyl group is obtained by 1) reacting compound (I) wherein corresponding R6 is substituted or unsubstituted phenyl group with chloro sulfonyl isocyanate, and 2) hydrolysing the obtained compound. The reaction of the compound (I) with the isocyanate compound can be carried out at between from 0°C to room temperature in suitable solvent such as CH2Cl2, THF acetonitrile or the like. Hydrolysis can be carried out by reaction with acid such as sulphuric acid hydrochloric acid, nitric acid or the like at between from room temperature to 100°C in a suitable solvent such as acetonitrile, water or the like.

(0126)

Step T

Conversion of alkanoyl group to imino alkyl group

The compound (I) wherein substituent of R1, R2, R3, R5 or R6 is hydroxyimino lower alkyl group or lower alkoxyimino lower alkyl group, is obtained by reacting compound (I) wherein substituent of corresponding R1, R2, R3, R5 or R6 is lower alkanoyl group with base such as acetic acid alkali metal salt such as NaOAc or the like in suitable solvent such as lower alcohol such as methanol, ethanol, PrOH, BuOH and acetonitrile or the like and hydroxyamine or lower alkoxyamine.

(0127)

Step U

Conversion to heterocyclic group of halogen atom

The compound (I) wherein R1, R2 or R3 is substituted or unsubstituted heterocyclic group is obtained by reacting compound (I) wherein corresponding R1, R2 or R3 is halogen atom with substituted or unsubstituted hetero cyclic boric acid using ordinary aryl coupling process such as Suzuki coupling process or the like. Coupling reaction can be carried out according to step in accordance with production method A.

(0128)

Step V

Oxidation of sulfur atom

Compound (I) wherein substituent of R6 is lower alkyl sulfinyl group, lower alkyl sulphonyl group, thiomorpholino lower alkyl S-oxide group or thiomorpholino-lower alkyl S, S-dioxide group is obtained by oxidising compound (I) wherein substituent of corresponding R6 is lower alkyl thio group or thiomorpholino lower alkyl group, at room temperature or while cooling

using oxidant such as mCPBA, hydrogen peroxide, peracid such as AcOOH or the like in a suitable solvent such as CH2Cl2 or the like.

(0129)

Step W

Imidation of hydroxy lower alkyl group

Compound (I) wherein substituent of R1, R2, R3 or R6 is lower alkyl group substituted by 2,5-dioxo-1-imidazolidinyl group optionally substituted by succinimide group or lower alkyl group is obtained by the imidation of compound (I) wherein the corresponding substituent R1, R2, R3 or R6 is hydroxy lower alkyl group. The imidation reaction is carried out can be carried out by conventional method such as Mitsunobu reaction or the like, cf the literature reference described in step F. The reaction is carried out by reacting the compound (I) at between from -20°C to 50°C in suitable organic solvent such as diethyl ether and THF with dilower alkyl azo dicarboxylate (for example diethylazo dicarboxylate), tri lower alkyl- or triarylphosphine (for example triphenylphosphine) and necessary imide such as hydantoin optionally substituted by lower alkyl group or succinimide.

(0130)

Effective component of this invention is exemplified in the following Production Examples, but it is not restricted to these.

Production Examples

Production Example 1

N-(2,6-dichlorobenzoyl)-4-(2-methoxyphenyl)-L-phenylalanine methyl ester (1A) and N-(2,6-dichlorobenzoyl)-4-(2-methoxyphenyl)-L-phenylalanine (1B).

1) Pyridine (3.58 ml) was added under nitrogen to N-(t-butoxycarbonyl)-L-tyrosine methyl ester (4.36 g) / anhydrous methylene chloride (100 ml) solution. The solution was cooled to 0°C, and anhydrous trifluoromethanesulfonic acid (3 ml) was added dropwise while stirring. On completion of the addition, ice bath was removed and the mixture was stirred at room temperature for three hours. The mixture was washed successively with water, 1N hydrochloric acid and water. The formed methylene chloride solution was washed with water subsequently to sodium bicarbonate aqueous solution, dried with magnesium sulfate, and was evaporated. The residue was refined by silica gel flash column chromatography (eluate, toluene / ethyl acetate (9 : 1)) and N-(t-butoxycarbonyl)-O-(trifluoromethane sulfonyl)-L-tyrosine methyl ester (6.2 g) was obtained.
ESMS: m/z 500 (MH^+).

2) To a toluene / DMF (25 mL /2.5 ml) mixture of 2-methoxybenzene boronic acid (0.446 g) and anhydrous potassium carbonate (0.84 g) was added the toluene (5 ml) solution of formed product (1.0 g) obtained as above under nitrogen. $Pd(PPH_3)_4$ (0.48 g) was added, and the mixture was heated at 80°C for 24 hours. The mixture was cooled, filtered with celite, and evaporation was caused. The residue was dissolved in ethyl acetate and was washed with water. The organic layer was dried with magnesium sulfate and evaporated, and crude substance was purified with silica gel flash column chromatography (eluate, ethyl acetate / hexane (1/3)), and N-(t-butoxycarbonyl)-4-(2-methoxyphenyl)-L-phenylalanine methyl ester (0.64 g) was obtained.
ESMS: m/z 386 (MH^+).

3) To methylene chloride (20 ml) solution of formed product (2.97 g) obtained as above was added TFA (20 ml), and the mixture was stirred for one hour 30 minutes. The solution was evaporated. The residue was dissolved in methylene chloride (20 ml) and the solution was evaporated. This step was repeated furthermore once again, and finally, residue was dried under a high vacuum, and 4-(2-methoxyphenyl)-L-phenylalanine methyl ester /TFA salt (2.93 g) was obtained.
ESMS: m/z 286 (MH^+).

4) To methylene chloride (30 ml) solution containing DIEA (2.24 g) of formed product (2.3 g) obtained as above was added while stirring 2,6-dichlorobenzoyl chloride (0.99 ml) solution at 0°C. The mixture was warmed to room temperature and stirred for 24 hours. The mixture was washed successively with water, 1N hydrochloric acid, saturated sodium bicarbonate and aqueous sodium chloride. The formed methylene chloride solution was dried with magnesium sulfate and evaporated, and purification with silica gel flash column chromatography (eluate, ethyl acetate /hexane (1/4)) was carried out on crude substance, and N-(2,6-dichlorobenzoyl)-4-(2-methoxyphenyl)-L-phenylalanine methyl ester (1.64 g) (1A) was obtained.
ESMS: m/z 458 (MH^+).

5) The formed product (0.1 g) obtained as above was dissolved in THF / methanol (5 mL /2 ml) liquid mixture. Water (2 ml) solution of LiOH (mono hydrate, 14 mg) was added, and the mixture was stirred at room temperature for three hours. The mixture was evaporated, and the residue was treated with water. Produced mixture was regulated to pH2 with 1N hydrochloric acid, and the mixture was extracted with ethyl acetate. The organic layer was washed with aqueous sodium chloride, dried and evaporated, and N-(2,6-dichlorobenzoyl)-4-(2-methoxyphenyl)-L-phenylalanine (0.08 g) (1B) was obtained.
ESMS: m/z 444 (MH+). mp. 211°C.

(0131)

Production Example 2

N-[(S)-2-phenyl propionyl]-4-(2-methoxyphenyl)-L-phenylalanine

1) DMF (5 ml) mixture of 4-(2-methoxyphenyl)-L-phenylalanine methyl ester / hydrochloride (0.03 g), (S)-2-phenylpropionic acid (0.014 g), EDC (0.02 g), HOBT (0.021 g) and DIEA (0.034 ml) was stirred at room temperature for 18 hours. DMF was eliminated, and the residue was distributed between ethyl acetate and water. The organic layer was evaporated, and it was washed successively with 10 % citric acid, saturated sodium bicarbonate and aqueous sodium chloride. The produced organic layer was dried with magnesium sulfate and evaporated, and silica gel flash column chromatography (eluate, methylene chloride / ethyl acetate (9 : 1)) purification was carried out on the residue, and N-[(S)-2-phenyl propionyl]-4-(2-methoxyphenyl)-L-phenylalanine methyl ester (0.031 g) was obtained.
ESMS: m/z 417 (MH^+).

2) The product (0.031 g) obtained as above was dissolved in THF / methanol (3 mL /0.3 ml) liquid mixture. 2N LiOH (0.07 ml) was added, and the mixture was stirred at room temperature for three hours. The mixture was evaporated, and the residue was treated with water. Produced mixture was regulated to pH2 with 1N hydrochloric acid, and the mixture was extracted with ethyl acetate. The organic layer was washed with aqueous sodium chloride, dried and evaporated, and the title compound (0.02 g) was obtained.
ESMS: m/z 403 (MH^+).

(0132)

Production Example 3

N-(2,6-difluoro benzoyl)-4-(2,6-dimethoxyphenyl)-L-phenylalanine.

1) 2,6-dimethoxybenzene boronic acid (0.5 g) was dissolved in DME (10 ml). Potassium carbonate (0.7 g), N-(t-butoxycarbonyl)-O-(trifluoromethane sulfonyl)-L-tyrosine methyl ester (0.4 g), Pd $(PPH_3)_4$ (0.6 g) and water (0.2 ml) were added to the said solution. Produced mixture was heated to 80°C overnight. Ethyl acetate and water were added to the said mixture successively. The ethyl acetate layer was dried with magnesium sulfate, and evaporation was caused. Silica gel flash column chromatography (eluate, ethyl acetate /hexane (1 : 2)) purification was carried out on the residue, and N-(t-butoxycarbonyl)-4-(2,6-dimethoxyphenyl)-L-phenylalanine methyl ester (380 mg) was obtained.

2) CF_3COOH (5 ml) was added to the product obtained as above, and the mixture was stirred at room temperature for four hours. The excess CF_3COOH was eliminated under reduced pressure. The residue was dissolved in methylene chloride and was washed with saturated sodium

bicarbonate. The organic layer was dried with magnesium sulfate, and evaporation was caused, and 4-(2,6-dimethoxyphenyl)-L-phenylalanine methyl ester (260 mg) was obtained.

3) The product (140 mg) obtained as above was dissolved in dried methylene chloride (10 ml). Et_3N (0.15 ml) and 2,6-difluoro benzoyl chloride (72 μl) were added to the said mixture, and the mixture was stirred at room temperature for six hours. Methylene chloride was added, and the organic layer was washed with water, dried with magnesium sulfate and evaporated. Silica gel flash column chromatography (eluate, ethyl acetate /hexane (1 : 2)) purification was carried out on the residue, and N-(2,6-difluoro benzoyl)-4-(2,6-dimethoxyphenyl)-L-phenylalanine methyl ester (160 mg) was obtained.
ESMS: m/z 455 (MH^+).

4) An aqueous solution (0.4 ml) of LiOH (mono hydrate, 12 mg) was added to THF (5 ml) solution of product (90 mg) obtained as above. Several drops of methanol were added, and the mixture was stirred overnight at room temperature. The excess organic solvent was eliminated under reduced pressure, and water was added to the residue, and the produced solution was acidified with 10 % citric acid. The produced solid was recovered by filtration, and it was washed with water, dried, and the title compound (70 mg) was obtained.
ESMS: m/z 441 (MH^+).

(0133)

Production Example 4

N-(2,6-dichlorobenzoyl)-4-(2-thienyl)-L-phenylalanine methyl ester (4A) and: N-(2,6-dichlorobenzoyl)-4-(2-thienyl)-L-phenylalanine (4B).

1) N-(t-butoxycarbonyl)-O-(trifluoromethane sulfonyl)-L-tyrosine methyl ester (3.42 g) dissolved in toluene (5 ml) was added under nitrogen to toluene / DMF (75 mL /7.5 ml) mixture of 2-thienyl boronic acid (1.135 g) and anhydrous potassium carbonate (2.23 g). $Pd(PPH_3)_4$ (1.4 g) was added, and the mixture was heated at 80°C for 24 hours. Silica gel flash column chromatography (eluate, ethyl acetate /hexane (1 : 3)) purification was carried out with crude substance after carrying out ordinary work up as described in Production Example 1, and N-(t-butoxycarbonyl)-4-(2-thienyl)-L-phenylalanine methyl ester (1.81 g) was obtained.
ESMS: m/z 362 (MH^+).

2) TFA (25 ml) was added to methylene chloride (25 ml) solution of product obtained as above (1.53 g), and the mixture was stirred at room temperature for one hour 30 minutes. The mixture was evaporated. The residue was distributed between methylene chloride (20 ml) and saturated sodium bicarbonate. The organic layer was separated, washed with aqueous sodium chloride, dried

with magnesium sulfate and evaporated, and 4-(2-thienyl)-L-phenylalanine methyl ester was obtained. The said free base was treated with diethyl ether solution of 10 % hydrochloric acid, and hydrochloride (1.036 g) was obtained.
ESMS: m/z 262 (MH^+).

3) Methylene chloride (1 ml) solution of 2,6-dichlorobenzoyl chloride (0.12 ml) was added to methylene chloride (5 ml) mixture containing DIEA (0.42 ml) of the hydrochloride (0.2 g) obtained as above at 0°C. The mixture was warmed to room temperature and was stirred for 24 hours, and washed successively with water, 1N hydrochloric acid, saturated sodium bicarbonate and aqueous sodium chloride. The organic layer was dried with magnesium sulfate and evaporated, and silica gel flash column chromatography (eluate, methylene chloride / ethyl acetate / hexane (1 : 1 : 6)) purification was carried out on the residue, and N-(2,6-dichlorobenzoyl)-4-(2-thienyl)-L-phenylalanine methyl ester (0.15 g) (4A) was obtained.
ESMS: m/z 434 (MH^+).

4) The product (0.1 g) obtained as above was dissolved in THF / methanol (5 mL /2 ml) liquid mixture. Aqueous solution (2 ml) of LiOH (mono hydrate, 14 mg) was added, and the mixture was stirred at room temperature for three hours. The mixture was evaporated, and the residue was treated with water. The mixture was regulated to pH2 with 1N hydrochloric acid, and extraction was carried out with ethyl acetate. The liquid extract was washed with aqueous sodium chloride and was dried with magnesium sulfate and evaporated, and N-(2,6-dichlorobenzoyl)-4-(2-thienyl)-L-phenylalanine (0.08 g) (4B) was obtained.
ESMS: m/z 420 (MH^+).

(0134)

Production Example 5

N-(2,6-dichlorobenzoyl)-4-(2-methoxyphenyl)-D-phenylalanine.

1) Methylene chloride (5 ml) solution of 2,6-dichlorobenzoyl chloride (0.68 ml) was added to D-tyrosine methyl ester / hydrochloride (1.0 g) solution and ice cooled solution of methylene chloride (15 ml) of DIEA (2.26 ml). The mixture was stirred at room temperature for 24 hours. The mixture was diluted with methylene chloride (50 ml), and washed successively with water, 1N hydrochloric acid and aqueous sodium chloride. The organic layer was dried with magnesium sulfate and evaporated, and the residue was recrystallized (from ethyl acetate / hexane), and N-(2,6-dichlorobenzoyl)-D-tyrosine methyl ester (1.46 g) was obtained.
ESMS: m/z 369 (MH^+).

2) To ice cooled solution of methylene chloride (0.33 ml) of the product (0.5 g) obtained as

above which contained pyridine (0.33 ml) was added slowly anhydrous trifluoromethanesulfonic acid (0.27 ml). The mixture was stirred for two hours 30 minutes, and it was washed successively with water, 1N hydrochloric acid, saturated sodium bicarbonate and water. The organic layer was dried with magnesium sulfate and evaporated, and silica gel flash column chromatography (eluate, toluene / ethyl acetate (9 : 1)) purification was carried out on the residue, and N-(2,6-dichlorobenzoyl)-O-(trifluoromethane sulfonyl)-D-tyrosine methyl ester (0.65 g) was obtained.
ESMS: m/z 501 (MH^+).

3) $Pd(PPH_3)_4$ (0.09 g) was added under nitrogen to toluene / DMF (4 mL /0.4 ml) suspension of 2-methoxybenzene boronic acid (0.082 g), potassium carbonate (0.16 g) and the product obtained as above (0.214 g). The mixture was heated at 80°C for 24 hours, and it was cooled and filtered, and the solvent was evaporated. The residue was dissolved in ethyl acetate, washed with water, dried with magnesium sulfate, and evaporation was caused. Silica gel flash column chromatography (eluate, toluene / ethyl acetate (10 : 1)) purification was carried out with the crude product, and N-(2,6-dichlorobenzoyl)-4-(2-methoxyphenyl)-D-phenylalanine methyl ester (45 mg) was obtained.
ESMS: m/z 458 (MH^+).

4) The product (90 mg) obtained as above was hydrolysed using LiOH in the same way as described in the production method of Production Example 1, and the title compound (25 mg) was obtained.
ESMS: m/z 444(MH+). mp. 195°C.

(0135)

Production Example 6

N-(2,6-dichlorobenzoyl)-3-(2-methoxyphenyl)-D,L-phenylalanine.

The title compound was obtained according to the production method same as Production Example 5.
ESMS: m/z 444 (MH+). mp. 104°C.

(0136)

Production Example 7

N-(2,6-dichlorobenzoyl)-4-(2,6-dimethoxyphenyl)-L-phenylalanine methyl ester (7A) and N-(2,6-dichlorobenzoyl)-4-(2,6-dimethoxyphenyl)-L-phenylalanine (7B).

1) 1,3-dimethoxybenzene (4 g) was dissolved in THF (10 ml) which had been freshly distilled. This solution was cooled to -78°C, and n-BuLi (24 mL, 1.6M hexane solution) was added dropwise to the said cold solution. The mixture was stirred at -78°C for one hour and thereafter,

it was warmed to room temperature and was stirred for one hour. Produced mixture was cooled to -78°C once again, and $(MeO)_3B$ (6.7 ml) was added. The mixture was warmed to room temperature, and it was stirred overnight. Water (10 ml) was added, and the mixture was stirred for 30 minutes and was made acidic to pH4 with acetic acid, and extraction was carried out with ethyl acetate. The said extract was dried with magnesium sulfate, and evaporation was caused, and 2,6-dimethoxybenzene boronic acid was obtained, and it was used without further refining.

2) The product (0.3 g) obtained as above and potassium carbonate (0.5 g) were suspended in DME (10 ml). N-(2,6-dichlorobenzoyl)-4-bromo-L-phenylalanine methyl ester (0.3 g), $Pd(PPh_3)_4$ (0.3g) and water (0.4 ml) were added to the said mixture, and the mixture was heated at 80°C for six hours. After cooling, ethyl acetate and water were added to the said mixture. The ethyl acetate layer was dried with magnesium sulfate, and evaporation was caused. Silica gel flash column chromatography (eluate, ethyl acetate /hexane (1 : 2)) purification was carried out on the residue, and N-(2,6-dichlorobenzoyl)-4-(2,6-dimethoxyphenyl)-L-phenylalanine methyl ester (0.2 g) (7A) was obtained.

3) The product (0.1 g) obtained as above was dissolved in dried THF (5 ml). Aqueous solution (0.5 ml) of LiOH (mono hydrate, 12 mg) and several drops of methanol were added to the said solution. The mixture was stirred at room temperature for two hours, and evaporation was caused. The residue was dissolved in water, and acidified with 10 % citric acid. The solid which was separated was recovered by filtration, and it was dried, and N-(2,6-dichlorobenzoyl)-4-(2,6-dimethoxyphenyl)-L-phenylalanine (80 mg) was obtained.
^{1}H-NMR (300 MHz, DMSO-d_6): δ 2.9 (dd, 1H), 3.2 (dd, 1H), 3.7 (s, 6H), 4.72 (m, 1H), 6.7 (d, 2H), 7.1-7.5 (m, 8H), 9.1 (d, 1H).
ESMS: m/z 474 (MH+), 472 ((M-H)-).

(0137)

Production Example 8

N-(2,6-dichlorobenzoyl)-4-(2-methoxyphenyl)-L-phenylalanine.

1) Hydrochloric acid gas was blown into ethanol (35 ml) solution of N-(t-butoxycarbonyl)-4-bromo-L-phenylalanine (5 g), and the mixture was left to stand at room temperature overnight. The solid which was separated was recovered by filtration, washed with ether and was air-dried, and 4-bromo-L-phenylalanine ethyl ester / hydrochloride (3.46 g) was obtained.
ESMS: m/z 274 (MH^+).

2) DIEA (6.1 ml) was added to methylene chloride (40 ml) suspension of the hydrochloride obtained as above (3.2 g) at 0°C. To said mixture, methylene chloride (5 ml) solution of 2,6-

dichlorobenzoyl chloride (2.0 ml) was added, and the mixture was stirred overnight at room temperature. The solvent was eliminated, and the residue was distributed with 1N hydrochloric acid and ethyl acetate. The organic layer was separated, washed with aqueous sodium chloride, and evaporated. Silica gel flash column chromatography (eluate, hexane / ethyl acetate (4 : 1)) purification was carried out on the formed product, and N-(2,6-dichlorobenzoyl)-4-bromo-L-phenylalanine ethyl ester (3.9 g) was obtained.
ESMS: m/z 446 (MH^+).

3) $Pd(PPh_3)_4$ (1.61 g) was added under argon to DME (50 ml) suspension of 2-methoxybenzene boronic acid (1.5 g), potassium carbonate (2.83 g) and product obtained as above (3.65 g). The mixture was heated at 80°C for 24 hours, and was cooled and filtered, and solvent was evaporated. The residue was dissolved in ethyl acetate, and the said ethyl acetate solution was washed with water, dried and evaporated. Silica gel flash column chromatography (eluate, hexane / ethyl acetate (4 : 1)) purification was carried out on the residue, and N-(2,6-dichlorobenzoyl)-4-(2-methoxyphenyl)-L-phenylalanine ethyl ester (2.1 g) was obtained.
ESMS: m/z 472 (MH^+).

4) Aqueous (1 ml) solution of LiOH (mono hydrate, 82 mg) was added to THF / methanol (5 mL /1 ml) solution of product obtained as above (0.4 g), and the mixture was stirred for one hour 30 minutes. The solvent was eliminated, and the residue was dissolved in water. The solution was acidified to pH2 with 1N hydrochloric acid, and the solid which was separated was recovered by filtration, washed with water and air-dried, and the title compound was thereby obtained. The following compounds (Production Examples 9-14) were produced using the same production method as in Production Example 7.

(0138)

Production Example 9

N-(2,6-dichlorobenzoyl)-4-(2,4-dimethoxyphenyl)-L-phenylalanine.
ESMS: m/z 474 (MH+), 472 ((M-H)-).

(0139)

Production Example 10

N-(2,6-dichlorobenzoyl)-4-(2,3,6-trimethoxyphenyl)-L-phenylalanine.
ESMS: m/z 504 (MH+), 502 ((M-H)-).

(0140)

Production Example 11

N-(2,6-dichlorobenzoyl)-4-(2,4,6-trimethoxyphenyl)-L-phenylalanine.

ESMS: m/z 504 (MH+), 502 ((M-H)-).

(0141)

Production Example 12

N-(2,6-dichlorobenzoyl)-4-(4-chloro-2,6-dimethoxyphenyl)-L-phenylalanine.

ESMS: m/z 509 (MH+), 507 ((M-H)-).

(0142)

Production Example 13

N-(2,6-dichlorobenzoyl)-4-(2,6-diethoxy phenyl)-L-phenylalanine.

ESMS: m/z 502 (MH+), 500 ((M-H)-).

(0143)

Production Example 14

N-(2,6-dichlorobenzoyl)-4-(2-ethoxy-6-methoxyphenyl)-L-phenylalanine.

ESMS: m/z 488 (MH+), 486 ((M-H)-).

(0144)

Production Example 15

N-(2,6-dichlorobenzoyl)-4-[2-[N-(t-butyl) sulphamoyl] phenyl]-L-phenylalanine methyl ester

2-[N-(t-butyl) sulphamoyl] benzene boronic acid (0.4 g) was dissolved in DME (10 ml). Potassium carbonate (0.1 g), N-(2,6-dichlorobenzoyl)-4-bromo-L-phenylalanine methyl ester (0.1 g), $Pd(PPh_3)_4$ (0.1g) and water (0.2 ml) were added to this solution. The mixture was heated at 80°C overnight. After cooling, ethyl acetate and water were added to the mixture. The ethyl acetate layer was dried with magnesium sulfate, and it was filtered and evaporated. Silica gel flash column chromatography (eluate, ethyl acetate / hexane (1 : 2)) purification was carried out on the residue, and the title compound (100 mg) was obtained.

ESMS: m/z 585.

(0145)

Production Example 16

N-(2,6-dichlorobenzoyl)-4-[2-[N-(t-butyl) sulphamoyl] phenyl]-L-phenylalanine

N-(2,6-dichlorobenzoyl)-4-[2-[N-(t-butyl) sulphamoyl] phenyl]-L-phenylalanine methyl ester (75 mg) was dissolved in THF (5 ml), and aqueous solution (0.4 ml) of LiOH (mono hydrate, 10 mg) was added to this solution. Several drops of methanol was added, and the mixture was stirred overnight at room temperature. The mixture was evaporated, and water was added to the said residue, and the mixture was acidified with 10 % citric acid. The solid which was separated was recovered by filtration, and was washed with water and dried, and the title compound (60 mg) was

obtained.

ESMS: m/z 549 (MH+), 547 ((M-H)-).

(0146)

Production Example 17

N-(2,6-dichlorobenzoyl)-4-(2-sulphamoyl phenyl)-L-phenylalanine.

1) N-(2,6-dichlorobenzoyl)-4-[2-[N-(t-butyl) sulphamoyl] phenyl]-L-phenylalanine methyl ester (130 mg) was dissolved in TFA (2 ml), and anisole (20 μM) was added to this solution, and the mixture was stirred at room temperature for six hours. TFA was eliminated under reduced pressure, and N-(2,6-dichlorobenzoyl)-4-(2-sulphamoyl phenyl)-L-phenylalanine methyl ester (100 mg) was obtained.

ESMS: m/z 507 (MH^+).

2) The product (100 mg) obtained as above was hydrolysed using the same procedures as in description of Production Example 16, and the title compound (80 mg) was obtained.

ESMS: m/z 493 (MH+), 491 ((M-H)-).

(0147)

Production Example 18

N-(2,6-dichlorobenzoyl)-4-[2-(N-benzoyl sulphamoyl) phenyl]-L-phenylalanine.

1) N-(2,6-dichlorobenzoyl)-4-(2-sulphamoyl phenyl)-L-phenylalanine methyl ester (100 mg) was dissolved in anhydrous pyridine (5 ml). Benzoyl chloride (50 μl) was added to this solution, and the mixture was stirred at room temperature under nitrogen for 12 hours. Ethyl acetate and saturated sodium bicarbonate were added to the said mixture, and the ethyl acetate layer was washed with 1N hydrochloric acid, dried with magnesium sulfate and evaporated. Silica gel flash column chromatography (eluate, ethyl acetate /hexane (1 : 2)) purification was carried out on the residue, and N-(2,6-dichlorobenzoyl)-4-[2-(N-benzoyl sulphamoyl) phenyl]-L-phenylalanine methyl ester was obtained.

2) The product obtained as above was hydrolysed using the same procedures as in description of Production Example 16, and the title compound (80 mg) was obtained.

ESMS: m/z 595 ((M-H)-).

(0148)

Production Example 19

N-(2,6-dichlorobenzoyl)-4-[2-(N-acetyl sulphamoyl) phenyl]-L-phenylalanine.

The title compound was produced using the same production method as in Production Example 18 except that benzoyl chloride was replaced with AcCl.

ESMS: m/z 533 ((M-H)-). The following compounds (Production Examples 20 and 21) were respectively produced using the same step and deprotection as in process outlined in Production Examples 15 and 16.

(0149)

Production Example 20

N-(2,6-dichlorobenzoyl)-4-[2-(N-methyl sulphamoyl) phenyl]-L-phenylalanine.

ESMS: m/z 505 ((M-H)-).

(0150)

Production Example 21

N-(2,6-dichlorobenzoyl)-4-[2-(N,N-dimethyl sulphamoyl) phenyl]-L-phenylalanine.

ESMS: m/z 519 ((M-H)-).

(0151)

Production Example 22

N-(2,6-dichlorobenzoyl)-4-[2-(t-butoxycarbonyl amino) phenyl]-L-phenylalanine.

1) 2-(t-butoxycarbonyl amino) benzene boronic acid (0.3 g) was subjected to a coupling reaction using N-(2,6-dichlorobenzoyl)-4-bromo-L-phenylalanine methyl ester (270 mg) by a production method same as in description of Production Example 15, and N-(2,6-dichlorobenzoyl)-4-[2-(t-butoxycarbonyl amino) phenyl]-L-phenylalanine methyl ester (250 mg) was obtained.

ESMS: m/z 543 (MH^+).

2) The product (40 mg) obtained as above was hydrolysed using the same procedures as in description of Production Example 16, and the title compound (35 mg) was obtained.

ESMS: m/z 529 (MH+), 527 ((M-H)-).

(0152)

Production Example 23

N-(2,6-dichlorobenzoyl)-4-(2-aminophenyl)-L-phenylalanine.

1) N-(2,6-dichlorobenzoyl)-4-[2-(t-butoxycarbonyl amino) phenyl]-L-phenylalanine methyl ester (90 mg) was treated at room temperature using TFA (1 ml) for two hours. The excess TFA was eliminated under vacuum, and N-(2,6-dichlorobenzoyl)-4-(2-aminophenyl)-L-phenylalanine methyl ester /TFA salt was obtained.

2) Produced TFA salt was hydrolysed using the same procedures as in description of Production Example 16, and the title compound (57 mg) was obtained.
ESMS: m/z 429 (MH^+).

(0153)

Production Example 24

N-(2,6-dichlorobenzoyl)-4-[2-(methanesulphonyl amino) phenyl]-L-phenylalanine.

1) N-(2,6-dichlorobenzoyl)-4-(2-aminophenyl)-L-phenylalanine methyl ester /TFA salt (90 mg) was dissolved in dried methylene chloride (5 ml). Et_3N (85 μl) and MsCl (30 μl) were added to this solution. The mixture was stirred at room temperature for three hours, and diluted with water. The organic layer was dried with magnesium sulfate, and evaporation was caused, and N-(2,6-dichlorobenzoyl)-4-[2-(methanesulphonyl amino) phenyl]-L-phenylalanine methyl ester was obtained.

2) The product obtained as above was hydrolysed using the same procedures as in description of Production Example 16, and the title compound (70 mg) was obtained.
ESMS: m/z 507 (MH+).

(0154)

Production Example 25

N-(2,6-dichlorobenzoyl)-4-[2-(acetylamino) phenyl]-L-phenylalanine.

1) N-(2,6-dichlorobenzoyl)-4-(2-aminophenyl)-L-phenylalanine methyl ester /TFA salt (90 mg) was dissolved in dried THF (5 ml). Acetic anhydride (60 μl) and DIEA (160 μl) were added, and the mixture was stirred at room temperature for 12 hours. Ethyl acetate was added, and the produced mixture was extracted with water. The organic layer was dried with magnesium sulfate, and evaporation was caused, and N-(2,6-dichlorobenzoyl)-4-[2-(acetylamino) phenyl]-L-phenylalanine methyl ester was obtained.

2) The product obtained as above was hydrolysed using the same procedures as in description of Production Example 16, and the title compound (60 mg) was obtained.
ESMS: m/z 471 (MH+).

(0155)

Production Example 26

N-(2,6-dichlorobenzoyl)-4-[2-(methoxycarbonylamino) phenyl]-L-phenylalanine.

1) N-(2,6-dichlorobenzoyl)-4-(2-aminophenyl)-L-phenylalanine methyl ester /TFA salt (90 mg) was dissolved in THF (5 ml), and DIEA (160 μl) and ClCOOMe (20 μl) were added to this solution. The mixture was stirred at room temperature for 12 hours. After carrying out usual work up shown in Production Example 25, N-(2,6-dichlorobenzoyl)-4-[2-(methoxycarbonylamino) phenyl]-L-phenylalanine methyl ester was obtained.

2) The product obtained as above was hydrolysed using the same procedures as in description of Production Example 16, and the title compound (70 mg) was obtained.
ESMS: m/z 487 (MH+).

(0156)

Production Example 27

N-(2,6-dichlorobenzoyl)-4-[2-(N,N-dimethylamino) phenyl]-L-phenylalanine.

1) N-(2,6-dichlorobenzoyl)-4-(2-aminophenyl)-L-phenylalanine methyl ester /TFA salt (90 mg) was dissolved in ethanol (5 ml). Formalin (96 μl), 1N hydrochloric acid (234 μl) and $NaCNBH_3$ (36 mg) were added to this solution. The mixture was stirred at room temperature for 30 minutes, and thereafter, mixture of ethanol (0.5 ml) and 1N hydrochloric acid (0.5 ml) (1 : 1) was added, and the mixture was stirred overnight. Furthermore, 1N hydrochloric acid was added and the mixture was stirred for 30 minutes. The mixture was neutralized with sodium bicarbonate and extraction was carried out with ethyl acetate. The liquid extract was combined and dried with magnesium sulfate, and evaporation was caused, and N-(2,6-dichlorobenzoyl)-4-[2-(N,N-dimethylamino) phenyl]-L-phenylalanine methyl ester was obtained.

2) The product obtained as above was hydrolysed using the same procedures as in description of Production Example 16, and the title compound (70 mg) was obtained.
ESMS: m/z 457 (MH+).

(0157)

Production Example 28

N-(2,6-dichlorobenzoyl)-4-(2-ureide phenyl)-L-phenylalanine.

1) N-(2,6-dichlorobenzoyl)-4-(2-aminophenyl)-L-phenylalanine methyl ester /TFA salt (90 mg) was dissolved in dried THF (5 ml). Chloro sulfonyl isocyanate (22 μL) was added to this solution, and the mixture was stirred at room temperature for two hours. The mixture was neutralized with sodium bicarbonate and extraction was carried out with ethyl acetate. The liquid extract was mixed and was dried with magnesium sulfate, and evaporation was caused.

2) The residue was hydrolysed using the same procedures as in description of Production Example 16, and HPLC (eluate, 60 % acetonitrile, 0.1 % CF_3COOH, 40 % water) purification was carried out, and the title compound (30 mg) was obtained.
ESMS: m/z 472 (MH+).

(0158)

Production Example 29

N-(2,6-dichlorobenzoyl)-4-[2-(N,N-dimethylamino)-6-methoxyphenyl]-L-phenylalanine.

1) 2-methoxy-6-(N,N-dimethylamino) benzene boronic acid was subjected to a coupling reaction with N-(2,6-dichlorobenzoyl)-4-bromo-L-phenylalanine methyl ester, and N-(2,6-dichlorobenzoyl)-4-[2-(N,N-dimethylamino)-6-methoxyphenyl]-L-phenylalanine methyl ester was obtained. Synthesis of said boronic acid and the said coupling reaction were carried out with a form same as in description of Production Example 7.

2) The product obtained as above was hydrolysed using the same procedures as in description of Production Example 7, and the title compound was thereby obtained.
ESMS: m/z 487 (MH+).

(0159)

Production Example 30

N-(2,6-dichlorobenzoyl)-4-(2-hydroxyphenyl)-L-phenylalanine.

1) BBr_3 (1 mL, 1M methylene chloride solution) was added while stirring at 0°C to methylene chloride (10 ml) solution of N-(2,6-dichlorobenzoyl)-4-(2-methoxyphenyl)-L-phenylalanine methyl ester (0.215 g), and the solution was warmed to room temperature slowly. The mixture was stirred for three hours, and the reaction was terminated with ethanol. The solvent was eliminated, and the residue was dissolved in ethyl acetate. The solution was washed with saturated sodium bicarbonate and then with aqueous sodium chloride, and was dried with magnesium sulfate, and evaporation was caused. Silica gel flash column chromatography (eluate, hexane / ethyl acetate (2 : 1)) purification was carried out on the residue, and N-(2,6-dichlorobenzoyl)-4-(2-hydroxyphenyl)-L-phenylalanine methyl ester (0.105 g) was obtained. ESMS: m/z 444 (MH+).

2) To THF / methanol (2 mL /0.2 mL) solution of product (0.03 g) obtained as above was added aqueous solution (0.2 ml) of LiOH (mono hydrate, 4 mg), and the mixture was stirred at room temperature for three hours. The solvent was eliminated, and the residue was dissolved in water. The mixture was acidified to pH2 with 1N hydrochloric acid, and a precipitated solid was

recovered by filtration, washed with water, air-dried, and the title compound (0.025 g) was obtained.

ESMS: m/z 430 (MH+).

(0160)

Production Example 31

N-(2,6-dichlorobenzoyl)-4-(2-hydroxy-6-methoxyphenyl)-L-phenylalanine.

1) N-(2,6-dichlorobenzoyl)-4-(2,6-dimethoxyphenyl)-L-phenylalanine ethyl ester (0.16 g, produced by process same as in methyl ester body in accordance with Production Example 8) was dissolved in anhydrous methylene chloride (8 ml). The solution was cooled to -78°C, and BBr_3 (0.56 mL, 1M methylene chloride solution) was added. The mixture was warmed to 0°C and was stirred at said temperature for two hours. Continuing, mixture was warmed to room temperature, and the reaction was terminated with saturated sodium bicarbonate (5 ml). The mixture was stirred for one hour, and diluted with methylene chloride. The organic layer was dried with magnesium sulfate and concentration carried out. Silica gel flash column chromatography (eluate, ethyl acetate /hexane (1 : 2)) purification was carried out on the residue, and N-(2,6-dichlorobenzoyl)-4-(2-hydroxy-6-methoxyphenyl)-L-phenylalanine ethyl ester (40 mg) was obtained.

ESMS: m/z 488 (MH+).

2) The product obtained as above (0.04 g) was hydrolysed using the same procedures as in description of Production Example 1, and the title compound (35 mg) was obtained.

ESMS: m/z 460 (MH+).

(0161)

Production Example 32

N-(2,6-dichlorobenzoyl)-4-[2-(carboxymethoxy) phenyl]-L-phenylalanine.

1) Cs_2CO_3 (0.11 g) was added under nitrogen to DMF (2 ml) solution of the product (0.1 g) obtained in Production Example 30-1) and the mixture was stirred for 30 minutes. DMF (1 ml) solution of $BrCH_2CO_2Me$ (61 ml) was added, and the mixture was stirred at 50°C for six hours. DMF was eliminated, and the residue was distributed between ethyl acetate and water. The ethyl acetate layer was washed with aqueous sodium chloride and was dried with magnesium sulfate, and evaporation was caused. Silica gel flash column chromatography (eluate, hexane / ethyl acetate (1 : 1)) purification was carried out on the residue, and N-(2,6-dichlorobenzoyl)-4-[2-(methoxycarbonyl methoxy) phenyl]-L-phenylalanine methyl ester (0.86 mg) was obtained.

ESMS: m/z 516 (MH+).

2) The product obtained as above (0.86 g) was hydrolysed using the same procedures as in description of Production Example 1, and the title compound (0.6 g) was obtained.
ESMS: m/z 488 (MH+).

(0162)

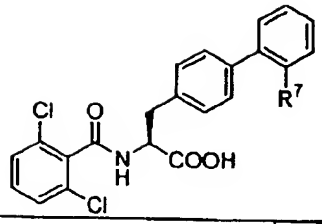
Production Example 33

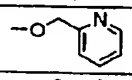
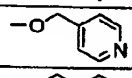
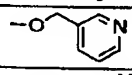
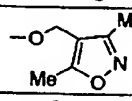
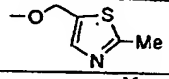
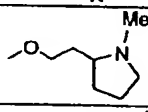
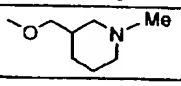
N-(2,6-dichlorobenzoyl)-4-[2-(cyano methoxy) phenyl]-L-phenylalanine methyl ester

The title compound was produced using the same procedures as in description of Production Example 32 starting from the N-(2,6-dichlorobenzoyl)-4-(2-hydroxyphenyl)-L-phenylalanine methyl ester and bromo acetonitrile.
ESMS: m/z 483 (MH+). The following compounds were obtained by similar process as in Production Example 32 by reacting with the necessary halide compound starting from the N-(2,6-dichlorobenzoyl)-4-(2-hydroxyphenyl)-L-phenylalanine methyl ester.

(0163)

Table 1



Production Example	R^7	m/z (MH+)
34	$-O(CH_2)_3CH_3$	486
35	$-OCH_2CH(Me)_2$	486
36	$-O(CH_2)_3CO_2H$	516
37	$-O(CH_2)_3OH$	488
38		521
39		521
40		521
41		539
42		541
43		541
44		541

(0164)

Production Example 45

N-(2,6-dichlorobenzoyl)-4-(2-formylphenyl)-L-phenylalanine.

1) N-(2,6-dichlorobenzoyl)-4-(2-formylphenyl)-L-phenylalanine methyl ester was produced according to order same as in Production Example 1 except that 2-methoxybenzene boronic acid was replaced with 2-formyl benzene boronic acid.
ESMS: m/z 456 (MH+).

2) The product obtained as above (50.4 mg) was dissolved in THF (1.33 ml) and methanol (220 μl) liquid mixture. 1M LiOH (220 m L) was added, and the produced mixture was stirred at room temperature under nitrogen for two hours. Thereafter, water was added, and the mixture was acidified (about pH2) with 1N hydrochloric acid, extracted with ethyl acetate, dried with magnesium sulfate and evaporated. Silica gel flash column chromatography (chloroform, and then chloroform / methanol (10 : 1)) purification was carried out on the residue, and the title compound (46.8 mg) was obtained.

ESMS: m/z 442 (MH+).

(0165)

Production Example 46

N-(2,6-dichlorobenzoyl)-4-[2-[(phenylamino) methyl] phenyl]-L-phenylalanine.

1) N-(2,6-dichlorobenzoyl)-4-(2-formylphenyl)-L-phenylalanine methyl ester (49.1 mg) was dissolved in anhydrous methanol (1 ml) and anhydrous THF (0.5 ml) liquid mixture. Thereafter, aniline (58.8 μl), hydrochloric acid (53.8 μL, 4M dioxane solution) and 3Å molecular sieve was added, and the mixture was stirred at room temperature under nitrogen for one hour. Sodium cyanoborohydride (4.06 mg) was added, and the mixture was stirred for further 72 hours. PH of mixture was made about 2 using 1N hydrochloric acid in order to terminate the reaction. The mixture was diluted with water and neutralized with 1M potassium hydroxide. Thereafter, it was extracted with methylene chloride and organic extract were combined and dried (potassium carbonate), and evaporation was caused. Silica gel preparative TLC (eluate, methylene chloride) purification was carried out on the residue, and N-(2,6-dichlorobenzoyl)-4-[2-(phenylamino) methyl] phenyl]-L-phenylalanine methyl ester (21.2 mg) was obtained.
ESMS: m/z 533 (MH+).

2) The product obtained as above (21.2 mg) was hydrolysed using the same procedures as in description of Production Example 1. The mixture was acidified to pH4-5 with AcOH, extracted with ethyl acetate (5x20 mL), dried with magnesium sulfate, and evaporation was caused. Silica gel column chromatography (eluate, chloroform / methanol (10 : 1)) purification was carried out on the residue, and the title compound was thereby obtained.
ESMS: m/z 519 (MH+).

The following compounds (Production Examples 47 and 48) were produced with a form same as in description of Production Example 46.

(0166)

Production Example 47

N-(2,6-dichlorobenzoyl)-4-[2-(aminomethyl) phenyl]-L-phenylalanine.
ESMS: m/z 443 (MH+).

(0167)

Production Example 48

N-(2,6-dichlorobenzoyl)-4-[2-[(benzylamino) methyl] phenyl]-L-phenylalanine.
ESMS: m/z 533 (MH+).

(0168)

Production Example 49

N-(2,6-dichlorobenzoyl)-4-[2-(2-carboxy ethenyl) phenyl]-L-phenylalanine.

1) N-(2,6-dichlorobenzoyl)-4-(2-formylphenyl)-L-phenylalanine methyl ester (51.7 mg) and (triphenylphosphoranylidene) acetic acid methyl ester (75.8 mg) were dissolved in anhydrous toluene (1 ml) and the solution was stirred at 80°C under nitrogen for 18 hours. The mixture was cooled, and silica gel preparative TLC (eluate, hexane / ethyl acetate (2 : 1)) purification was carried out, and N-(2,6-dichlorobenzoyl)-4-[2-[2-(methoxycarbonyl) ethenyl] phenyl]-L-phenylalanine methyl ester (48.0 mg) was obtained.
ESMS: m/z 512 (MH+).

2) The product obtained as above (26.4 mg) was hydrolysed using LiOH hydrate (5 equivalents) with a form same as in description of Production Example 1, and the title compound (22.0 mg) was obtained as mixture of trans and cis isomer (4 : 1).
ESMS: m/z 484 (MH+).

(0169)

Production Example 50

N-(2,6-dichlorobenzoyl)-4-[2-(hydroxymethyl) phenyl]-L-phenylalanine.

1) $NaBH_4$ (21 mg) was added to N-(2,6-dichlorobenzoyl)-4-(2-formylphenyl)-L-phenylalanine methyl ester (0.23 g) dissolved in methanol (5 ml), and the mixture was stirred at room temperature for three hours. The reaction was terminated using acetone, and the mixture was evaporated. The residue was distributed between ethyl acetate and water. The ethyl acetate layer was dried with magnesium sulfate, and evaporation was caused, and N-(2,6-dichlorobenzoyl)-4-[2-(hydroxymethyl) phenyl]-L-phenylalanine methyl ester (0.24 g) was obtained.
ESMS: m/z 480 ((M+Na)+).

2) The product obtained as above was hydrolysed using the same procedures as in description of Production Example 1, and the title compound (0.2 g) was obtained.
ESMS: m/z 450 ((M+Li)+).

(0170)

Production Example 51

N-(2,6-dichlorobenzoyl)-4-[2-(methoxymethyl) phenyl]-L-phenylalanine.

1) Methylene chloride (5 ml) mixture of N-(2,6-dichlorobenzoyl)-4-[2-(hydroxymethyl) phenyl]-L-phenylalanine methyl ester (0.15 g), CBr_4 (0.22 g) and PPh_3 (0.173 g) was stirred at room temperature for 18 hours. The solvent was evaporated, and silica gel flash column chromatography (eluate, methylene chloride / ethyl acetate (9 : 1)-(8 : 1)) purification was carried out on the residue, and N-(2,6-dichlorobenzoyl)-4-[2-(bromomethyl) phenyl]-L-phenylalanine methyl ester (0.12 g) was obtained.
ESMS: m/z 522(MH+).

2) DMF (3 ml) mixture of product (0.04 g) obtained as above and NaOMe (0.04 g) was stirred at room temperature for 18 hours. DMF was eliminated, and the residue was distributed between ethyl acetate and water. The aqueous layer was separated, and it was regulated to pH4 with 1N hydrochloric acid and extraction was carried out with ethyl acetate. The said ethyl acetate layer was washed with aqueous sodium chloride, dried with magnesium sulfate, and evaporation was caused. HPLC (eluate, 60 % acetonitrile, 0.1 % CF_3COOH, 40 % water) purification was carried out on the residue, and the title compound (9.4 mg) was obtained.
ESMS: m/z 480 ((M+Na)+).

(0171)

Production Example 52

N-(2,6-dichlorobenzoyl)-4-(2-carboxy phenyl)-L-phenylalanine.

1) N-(2,6-dichlorobenzoyl)-4-(2-formylphenyl)-L-phenylalanine methyl ester (104 mg) was dissolved in acetone (700 μl) by heating to about 40°C. Thereafter, mixed solution of acetone (900 μl) of $KMnO_4$ (61.2 mg) and water (130 μl) which was warmed to 40°C was added over a period of one hour, and the produced mixture was stirred at the same temperature for further two hours. The mixture was filtered with celite and was washed with acetone. The filtrate was dissolved in water, acidified to about pH2 with 1N hydrochloric acid, and extraction was carried out with ethyl acetate. The liquid extract was combined, dried with magnesium sulfate, and evaporation was caused. Silica gel column (eluate, toluene, and then toluene / ethyl acetate (gradient from 20 : 1 to 3 : 1)) purification was carried out on the residue, and N-(2,6-dichlorobenzoyl)-4-(2-carboxy phenyl)-L-phenylalanine methyl ester (85.0 mg) was obtained.
ESMS: m/z 472(MH+).

2) The product obtained as above was hydrolysed using the same procedures as in description of Production Example 1, and the title compound (34.1 mg) was obtained.
ESMS: m/z 458 (MH+).

(0172)

Production Example 53

N-(2,6-dichlorobenzoyl)-4-[2-(N-benzyl carbamoyl) phenyl]-L-phenylalanine.

1) N-(2,6-dichlorobenzoyl)-4-(2-carboxy phenyl)-L-phenylalanine methyl ester (51.9 mg) was dissolved in anhydrous DMF (1 ml), and EDC (25.3 mg), HOBT (20.2 mg), DIEA (28.7 μl) and benzylamine (14.4 μl) were added. Produced mixture was stirred at room temperature under nitrogen for 20 hours, and it was diluted using ethyl acetate and washed with 1N hydrochloric acid, saturated sodium bicarbonate, water and aqueous sodium chloride. The organic layer was dried with magnesium sulfate, and evaporation was caused. Silica gel column (eluate, hexane / ethyl acetate (1 : 1- 1: 2)) purification was carried out on the residue, and N-(2,6-dichlorobenzoyl)-4-[2-(N-benzyl carbamoyl) phenyl]-L-phenylalanine methyl ester (48.9 mg) was obtained.
ESMS: m/z 561 (MH+).

2) The product obtained as above was hydrolysed using the same procedures as in description of Production Example 1, and the title compound (34.2 mg) was obtained.
ESMS: m/z 547 (MH+).

The following compounds (Production Examples 54-59) were produced with similar form as described in Production Example 53.

(0173)

Production Example 54

N-(2,6-dichlorobenzoyl)-4-[2-(N-methylcarbamoyl) phenyl]-L-phenylalanine.
ESMS: m/z 471 (MH+).

(0174)

Production Example 55

N-(2,6-dichlorobenzoyl)-4-[2-(N-n-butyl carbamoyl) phenyl]-L-phenylalanine.
ESMS: m/z 513 (MH+).

(0175)

Production Example 56

N-(2,6-dichlorobenzoyl)-4-[2-[N-(2-hydroxyethyl) carbamoyl] phenyl]-L-phenylalanine.
ESMS: m/z 501 (MH+).

(0176)

Production Example 57

N-(2,6-dichlorobenzoyl)-4-[2-[N-(3-hydroxypropyl) carbamoyl] phenyl]-L-phenylalanine.

ESMS: m/z515 (MH+).

(0177)

Production Example 58

N-(2,6-dichlorobenzoyl)-4-[2-(N,N-dimethylcarbamoyl) phenyl]-L-phenylalanine.

ESMS: m/z 485 (MH+).

(0178)

Production Example 59

N-(2,6-dichlorobenzoyl)-4-[2-[N-(2-morpholinoethyl) carbamoyl] phenyl]-L-phenylalanine.

ESMS: m/z 570 (MH+).

(0179)

Production Example 60

N-(2,6-dichlorobenzoyl)-4-[2-(carbamoyl) phenyl]-L-phenylalanine.

1) N-(2,6-dichlorobenzoyl)-4-(2-carboxy phenyl)-L-phenylalanine methyl ester (52.6 mg) was dissolved in anhydrous THF (1 ml), and carbonyldiimidazole (36.1 mg) was added, and the mixture was stirred at room temperature under nitrogen for two hours. Ammonium hydroxide (29 % aqueous solution, 135 μL) was added, and the mixture was stirred for further 22 hours. Thereafter, mixture was extracted with ethyl acetate. The said extract was washed with 1N hydrochloric acid, saturated sodium bicarbonate and aqueous sodium chloride, dried with magnesium sulfate, and evaporation was caused. Silica gel column (eluate, toluene / ethyl acetate (1 : 1)) purification was carried out on the residue, and N-(2,6-dichlorobenzoyl)-4-(2-carbamoyl phenyl)-L-phenylalanine methyl ester (48.1 mg) was obtained.
ESMS: m/z 471 (MH+).

2) The product obtained as above was hydrolysed using LiOH (3 equivalents) with a form same as in description of Production Example 1, and the title compound (41.6 mg) was obtained. ESMS: m/z 457 (MH+).

(0180)

Production Example 61

N-(2,6-dichlorobenzoyl)-4-[2-[(N-methanesulphonyl) carbamoyl] phenyl]-L-phenylalanine.

1) N-(2,6-dichlorobenzoyl)-4-(2-carboxy phenyl)-L-phenylalanine methyl ester (57.0 mg) was dissolved in anhydrous THF (1 ml), and carbonyldiimidazole (23.5 mg) was added, and the mixture was stirred at room temperature under nitrogen for two hours. Methane sulfonamide

(17.2 mg) and DBU (27 μl) were added, and the mixture was stirred for further 18 hours. Thereafter, mixture was heated to 40°C, and stirred at said temperature for seven hours, and it was cooled to room temperature, diluted with ethyl acetate and was washed with 1N hydrochloric acid, and thereafter, washed with aqueous sodium chloride, dried with magnesium sulfate, and evaporation was caused. Silica gel preparative TLC (eluate, methylene chloride : methanol (100 : 1-10 : 1)) purification was carried out on the residue, and N-(2,6-dichlorobenzoyl)-4-[2-[N-(methanesulphonyl) carbamoyl] phenyl]-L-phenylalanine methyl ester (37.0 mg) was obtained.
ESMS: m/z 549 (MH+).

2) The product obtained as above was hydrolysed using LiOH (3 equivalents) with a form same as in description of Production Example 1, and the title compound (36 mg) was obtained.
ESMS: m/z 535 (MH+).

(0181)

Production Example 62

N-(2-chloro-4-nitrobenzoyl)-4-(2-methoxyphenyl)-L-phenylalanine.

1) N-(2-chloro-4-nitrobenzoyl)-4-(2-methoxyphenyl)-L-phenylalanine methyl ester was produced using the same procedures as in the process described in Production Examples 1-1), 2), 3) and 4) except that 2,6-dichlorobenzoyl chloride was replaced by 2-chloro-4-nitrobenzoyl chloride.

2) Thereafter, said methyl ester body obtained as above was hydrolysed using the same procedures as in description of Production Example 1-5) and the title compound was obtained.
ESMS: m/z 455 (MH+).

(0182)

Production Example 63

N-(4-amino-2-chlorobenzoyl)-4-(2-methoxyphenyl)-L-phenylalanine.

1) Raney nickel (0.4 mL, 50 % dispersed in water) was added to anhydrous methanol (50 ml) solution of N-(2-chloro-4-nitrobenzoyl)-4-(2-methoxyphenyl)-L-phenylalanine methyl ester (1.04 g), and the mixture was stirred at room temperature under H_2 atmosphere for three hours 30 minutes. Thereafter, mixture was filtered with celite and washed with methanol. The filtrate was evaporated, and silica gel flash column chromatography (eluate, methylene chloride/methanol (100 : 1-20 : 1)) purification was carried out on the residue, and N-(4-amino-2-chlorobenzoyl)-4-(2-methoxyphenyl)-L-phenylalanine methyl ester (887 mg) was produced.
ESMS: m/z 439 (MH+).

Aforesaid compound can be also produced by the coupling reaction of 4-(2-methoxyphenyl)-L-phenylalanine methyl ester / hydrochloride with 4-amino-2-chlorobenzoic acid but otherwise the procedures were similar to those described in Production Example 2 using EDC and HOBT.

2) The product obtained as above (57.0 mg) was hydrolysed using LiOH in liquid mixture of THF / methanol using the same procedures as in the description of Production Example 1-5). The solvent was eliminated, and the residue was dissolved in water. The mixture was acidified to about pH5 using 10 % citric acid, extracted with ethyl acetate, dried with magnesium sulfate and it was evaporated. Silica gel column (eluate, chloroform / methanol (10 : 1)) purification was carried out on the residue, and the title compound (53.9 mg) was obtained.
ESMS: m/z 425 (MH+).

(0183)

Production Example 64

N-[2-chloro-4-(methanesulphonyl amino) benzoyl]-4-(2-methoxyphenyl)-L-phenylalanine.

1) $MeSO_2Cl$ (24 μl) was added to anhydrous methylene chloride (1 ml) solution containing DIEA (66.6 μl) of N-(4-amino-2-chlorobenzoyl)-4-(2-methoxyphenyl)-L-phenylalanine methyl ester (56.0 mg). Produced mixture was stirred at room temperature under nitrogen for three hours, and it was diluted with methylene chloride, washed with 1N hydrochloric acid and water, dried with magnesium sulfate, and evaporation was caused. Silica gel column (eluate, methylene chloride) purification was carried out on the residue, and N-[2-chloro-4-(N,N-dimethane sulfonyl amino) benzoyl]-4-(2-methoxyphenyl)-L-phenylalanine methyl ester (59.4 mg) was obtained.
ESMS: m/z 595 (MH+).

2) The product obtained as above was hydrolysed using LiOH (3 equivalents) with a form same as in description of Production Example 1-5) and the title compound (43.4 mg) was obtained.
ESMS: m/z 503 (MH+).

The following compounds (Production Examples 65-68) were produced with a similar form as described in Production Example 64.

(0184)

Production Example 65

N-[2-chloro-4-(trifluoromethane sulfonyl amino) benzoyl]-4-(2-methoxyphenyl)-L-phenylalanine.
ESMS: m/z 557 (MH+). $MeSO_2Cl$ was replaced by CF_3SO_2Cl.

(0185)

Production Example 66

N-[2-chloro-4-(ethoxycarbonylamino) benzoyl]-4-(2-methoxyphenyl)-L-phenylalanine.

ESMS: m/z 497 (MH+). $MeSO_2Cl$ was replaced by EtOCOCl.

(0186)

Production Example 67

N-[2-chloro-4-(acetylamino) benzoyl]-4-(2-methoxyphenyl)-L-phenylalanine.

ESMS: m/z 467 (MH+). $MeSO_2Cl$ was replaced by AcCl.

(0187)

Production Example 68

N-[2-chloro-4-(benzensulphonyl amino) benzoyl]-4-(2-methoxyphenyl)-L-phenylalanine.

ESMS: m/z 565 (MH+). $MeSO_2Cl$ was replaced by $PhSO_2Cl$.

(0188)

Production Example 69

N-(2-chloro-4-ureide benzoyl)-4-(2-methoxyphenyl)-L-phenylalanine.

1) Chloro sulfonyl isocyanate (16.4 μl) was added to anhydrous acetonitrile (1 ml) solution of N-(4-amino-2-chlorobenzoyl)-4-(2-methoxyphenyl)-L-phenylalanine methyl ester (55.2 mg), and the mixture was stirred at room temperature under nitrogen for one hour. Saturated sodium bicarbonate (40 ml) was added slowly, and the mixture was extracted with ethyl acetate. The liquid extract were combined, dried with magnesium sulfate, and evaporation was caused. Silica gel preparative TLC (eluate, chloroform / methanol) purification was carried out with the residue.

2) The product obtained as above was hydrolysed using LiOH with a form same as in description of Production Example 64, and the title compound (24 mg) was obtained.

ESMS: m/z 468 (MH+).

(0189)

Production Example 70

N-[2-chloro-4-(3-methylthio ureide) benzoyl]-4-(2-methoxyphenyl)-L-phenylalanine.

1) Methyl isothiocyanate (43 μl) was added to anhydrous DMF (1 ml) solution containing DMAP (catalytic quantity) and DIEA (22 μl) of N-(4-amino-2-chlorobenzoyl)-4-(2-methoxyphenyl)-L-phenylalanine methyl ester (55.1 mg). Thereafter, the produced mixture was heated at 90°C under nitrogen for a whole day. After cooling, mixture was diluted with ethyl acetate, washed

successively with 1N hydrochloric acid, saturated sodium bicarbonate and water, dried with magnesium sulfate, and evaporation was caused. Silica gel preparative TLC (eluate, methylene chloride / methanol (15 : 1)) purification was carried out on the residue, and N-[2-chloro-4-(3-methylthio ureide) benzoyl]-4-(2-methoxyphenyl)-L-phenylalanine methyl ester (22.7 mg) was obtained.
ESMS: m/z 512 (MH+).

2) The product obtained as above was hydrolysed using the same procedures as in description of Production Example 64, and the title compound (22.0 mg) was obtained.
ESMS: m/z 498 (MH+).

(0190)

Production Example 71

3-acetyl-N-(2,6-dichlorobenzoyl)-4-(2-methoxyphenyl)-L-phenylalanine.

1) 3-acetyl-L-tyrosine ethyl ester was produced by blowing hydrochloric acid gas in ethanol (30 ml) solution of 3-acetyl-L-tyrosine (5 g). Di-t-butyl dicarbonate (5 g) was added to THF (50 ml) and DIEA (10 ml) solution of 3-acetyl-L-tyrosine ethyl ester (5 g), and the mixture was stirred overnight at room temperature. THF was eliminated, and the residue was distributed with water and methylene chloride. The organic layer was separated, dried with magnesium sulfate, and evaporation was caused. Silica gel flash column chromatography (eluate, hexane / ethyl acetate (4 : 1)) purification was carried out on the residue, and N-(t-butoxycarbonyl)-3-acetyl-L-tyrosine ethyl ester (4.3 g) was obtained.
ESMS: m/z 352 (MH+).

2) Anhydrous pyridine (1.1 mL, 12.82 mmol) was added with stirring at 0°C to methylene chloride (15 ml) solution of product (1.5g) obtained as above. Anhydrous trifluoromethanesulfonic acid (1.1 ml) was added dropwise, and the mixture was warmed to room temperature slowly and was stirred for 24 hours. The mixture was diluted with methylene chloride, washed successively with 1N hydrochloric acid, aqueous sodium chloride, saturated sodium bicarbonate and aqueous sodium chloride, dried with magnesium sulfate, and evaporation was caused, and N-(t-butoxycarbonyl)-3-acetyl-O-(trifluoromethane sulfonyl)-L-tyrosine ethyl ester (2.5 g) was obtained.
ESMS: m/z 506 ((M+Na)+).

3) The product obtained as above (0.3g) dissolved in toluene (3 ml) was added to toluene / DMF (4/1 mL) solution of 2-methoxybenzene boronic acid (0.13 g) and potassium carbonate (0.25 g) under nitrogen while stirring. $Pd(PPh_3)_4$ (0.14 g) was added, and the mixture was heated at 85°C

for 48 hours. The mixture was cooled and filtered, and the solvent was evaporated. The residue was dissolved in ethyl acetate, washed with water and dried with magnesium sulfate, and evaporation was caused. Silica gel flash column chromatography (eluate, hexane / ethyl acetate (2.5 : 1)) purification was carried out on the residue, and 3-acetyl-N-(t-butoxycarbonyl)-4-(2-methoxyphenyl)-L-phenylalanine ethyl ester (0.18 g) was obtained.
ESMS: m/z 442 (MH+).

4) TFA / methylene chloride (8 mL, 50 % v / v) solution of product obtained as above (0.18 g) was stirred at room temperature for one hour. The solution was evaporated, and dried under a high vacuum, and 3-acetyl-4-(2-methoxyphenyl)-L-phenylalanine ethyl ester / TFA salt was obtained.

5) To ice cooled solution of methylene chloride (2 ml) of said TFA salt obtained as above were added DIEA (213 μl) and continuingly 2,6-dichlorobenzoyl chloride (65 ml) / methylene chloride (7 ml) solution. The mixture was warmed to room temperature and was stirred for 24 hours. After carrying out the ordinary work up as described in Production Example 1-4), silica gel flash column chromatography (eluate, hexane / ethyl acetate (3 : 1)) purification was carried out with crude substance, and obtained 3-acetyl-N-(2,6-dichlorobenzoyl)-4-(2-methoxyphenyl)-L-phenylalanine ethyl ester (0.142 g).
ESMS: m/z 514 (MH+).

6) The product obtained as above (0.05 g) was hydrolysed using LiOH by a production method same as in description of Production Example 1-5) and the title compound (46.5 mg) was obtained.
mp. 87-89°C. ESMS: m/z 486 (MH+).

(0191)

Production Example 72

3-acetyl-N-(2,6-dichlorobenzoyl)-4-phenyl-L-phenylalanine

With a form same as in description of Production Example 71 except that 2-methoxybenzene boronic acid was replaced by benzene boronic acid, the solid state title compound was obtained.
mp. 109-111°C. ESMS: m/z 456 (MH+).

(0192)

Production Example 73

N-(2,6-dichlorobenzoyl)-3-(1-hydroxyethyl)-4-(2-methoxyphenyl)-L-phenylalanine.

1) $NaBH_4$ (12 mg) was added to 3-acetyl-N-(2,6-dichlorobenzoyl)-4-(2-methoxyphenyl)-L-

phenylalanine ethyl ester (0.1 g) / methanol (3 ml) solution, and the mixture was stirred at room temperature for two hours. The reaction of the mixture was terminated with 1N hydrochloric acid, and extraction was carried out with methylene chloride. (sic). The liquid extract was washed successively with 1N hydrochloric acid and aqueous sodium chloride, dried, and evaporation was caused. Silica gel flash column chromatography (eluate, hexane / ethyl acetate (3 : 1)) purification was carried out on the residue, and N-(2,6-dichlorobenzoyl)-3-(1-hydroxyethyl)-4-(2-methoxyphenyl)-L-phenylalanine ethyl ester (45 mg) was obtained.
ESMS: m/z 516 (MH+).

2) The product obtained as above (0.040 g) was hydrolysed using LiOH with a form same as in description of Production Example 1-5) and the title compound (28 mg) was obtained.
ESMS: m/z 488 (MH+).

(0193)

Production Example 74

N-(2,6-dichlorobenzoyl)-3-(1-hydroxyethyl)-4-phenyl-L-phenylalanine.

The title compound was produced from the 3-acetyl-N-(2,6-dichlorobenzoyl)-4-phenyl-L-phenylalanine ethyl ester by a process same as in description of Production Example 73.
mp. 115-117°C. MS: m/z 458 (MH+).

(0194)

Production Example 75

N-(2,6-dichlorobenzoyl)-3-methoxy-4-(2-methoxyphenyl)-L-phenylalanine.

1) 3,4-dihydroxy-L-phenylalanine methyl ester was produced by blowing hydrochloric acid in 3,4-dihydroxy-L-phenylalanine (10 g) dissolved in methanol (100 ml). Di-t-butyl dicarbonate (12.1 g) was added to THF (250 ml) and DIEA (35.4 ml) solution of said ester, and the mixture was warmed for five minutes and was stirred at room temperature for one hour. THF was eliminated, and the residue was distributed with water and ethyl acetate. The organic layer was washed with 1N hydrochloric acid and aqueous sodium chloride, dried with magnesium sulfate, and evaporation was caused. Silica gel flash column chromatography (eluate, hexane / ethyl acetate (1 : 1)) purification was carried out on the residue, and the target N-(t-butoxycarbonyl)-3, 4-dihydroxy-L-phenylalanine methyl ester (13.4 g) was obtained.
ESMS: m/z 312 (MH+).

2) 2,6-dichlorobenzyl chloride (17.3 g) was added at room temperature to DMF (15 ml) suspension of N-(t-butoxycarbonyl)-3,4-dihydroxy-L-phenylalanine methyl ester (2.5 g), potassium carbonate (2.22 g) and n-Bu_4NI (0.297 g). The mixture was stirred at room

temperature overnight, and it was diluted with water, and extraction was carried out with ether. The liquid extract was dried with magnesium sulfate, and evaporation was caused. Silica gel column chromatography (eluate, hexane / methylene chloride / ethyl acetate (5 : 5 : 1)) purification was carried out on the residue, and N-(t-butoxycarbonyl)-3,4-bis (2,6-dichlorobenzyl oxy)-L-phenylalanine methyl ester (2.0 g, ESMS: m/z 630 (MH+)), N-(t-butoxycarbonyl)-3-(2,6-dichlorobenzyl oxy)-4-hydroxy-L-phenylalanine methyl ester (0.39 g, ESMS: m/z 470 (MH+)) and N-(t-butoxycarbonyl)-4-(2,6-dichlorobenzyl oxy)-3-hydroxy-L-phenylalanine methyl ester (0.45 g, ESMS: m/z 470 (MH+)) were obtained respectively.

3) Methyl iodide (0.072 ml) was added to DMF (4.0 ml) suspension of N-(t-butoxycarbonyl)-4-(2,6-dichlorobenzyl oxy)-3-hydroxy-L-phenylalanine methyl ester (0.45 g), potassium carbonate (0.199 g) and n-Bu_4NI (0.035 g), and the mixture was stirred overnight at room temperature. DMF was eliminated, and the residue was distributed with water and ethyl acetate. The organic layer was separated, and aqueous solution was extracted with ethyl acetate. The liquid extract were combined, dried with magnesium sulfate, and evaporation was caused. Silica gel preparative TLC (eluate, hexane / methylene chloride ethyl acetate (3 : 3 : 1)) purification was carried out on the residue, and N-(t-butoxycarbonyl)-4-(2,6-dichlorobenzyl oxy)-3-methoxy-L-phenylalanine methyl ester (0.396 g) was obtained.
ESMS: m/z 484 (MH+).

4) To methanol (10 ml) suspension of 10 % Pd-carbon and product obtained as above (0.39 g) was blown hydrogen gas at room temperature overnight. The catalyst was filtered with celite, and the filtrate was evaporated. Silica gel preparative TLC (eluate, methylene chloride / methanol (10 : 1)) purification was carried out on the residue, and N-(t-butoxycarbonyl)-4-hydroxy-3-methoxy-L-phenylalanine methyl ester (0.21 g) was obtained.
ESMS: m/z 348 ((M+Na)+).

5) Anhydrous pyridine (0.15 ml) was added while stirring at 0°C to methylene chloride (3.0 ml) solution of product obtained as above (0.2 g). Anhydrous trifluoromethanesulfonic acid (0.16 ml) was added dropwise, and the mixture was warmed to room temperature slowly and stirred at room temperature for three hours. The mixture was diluted with methylene chloride, washed successively with 1N hydrochloric acid, aqueous sodium chloride, saturated sodium bicarbonate and aqueous sodium chloride. The organic layer was dried with magnesium sulfate, and evaporation was caused, and N-(t-butoxycarbonyl)-3-methoxy-4-trifluoromethane sulfonyl oxy-L-phenylalanine methyl ester (0.28 g) was obtained.
ESMS: m/z 457 [(M + Na]+).

6) DME (2.0 ml) solution of product obtained as above (0.28 g) was added under nitrogen to

DME (2.0 ml) solution of 2-methoxybenzene boronic acid (0.112 g) and potassium carbonate (0.21 g). $Pd(PPh_3)_4$ (0.12g) was added, and the mixture was heated at 65°C for 48 hours, cooled, filtered, and solvent was evaporated. The residue was extracted with ethyl acetate, and the extract was washed with water, dried and evaporated. Silica gel preparative TLC (eluate, hexane / ethyl acetate (3 : 1)) purification was carried out on the residue, and N-(t-butoxycarbonyl)-3-methoxy-4-(2-methoxyphenyl)-L-phenylalanine methyl ester (0.02 g) was produced.
ESMS: m/z 438 ((M+Na)+).

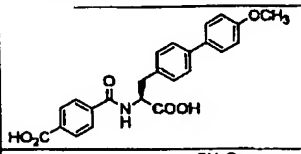
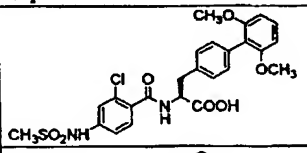
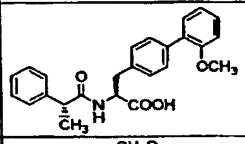
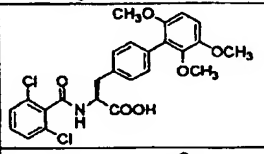
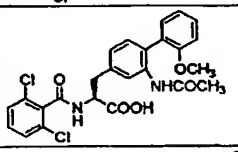
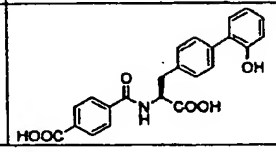
7) TFA / methylene chloride (1 mL, 50 % v / v) mixture of product obtained as above (0.055 g) was stirred at room temperature for one hour, evaporated and dried under a high vacuum. DIEA (0.069 ml) and continuingly, 2,6-dichlorobenzoyl chloride (0.02 ml) / methylene chloride (1 ml) solution were added to ice cooled solution of the residue methylene chloride (2 ml). The mixture was warmed to room temperature, and stirred overnight. After carrying out the ordinary work up with a form same as in Production Example 1, silica gel preparative TLC (eluate, hexane / ethyl acetate (2 : 1)) purification was carried out with crude substance, and the N-(2,6-dichlorobenzoyl)-3-methoxy-4-(2-methoxyphenyl)-L-phenylalanine methyl ester (0.04 g) was obtained.
ESMS: m/z 488 (MH+).

8) The product obtained as above (0.04 g) was hydrolysed using LiOH with a form same as in description of Production Example 1-5) and the title compound (17.8 mg) was obtained.
mp. 100-102°C. ESMS: m/z 474 (MH+).

The following compounds were produced from the corresponding substances in the same way as in process described in the aforesaid Production Examples.

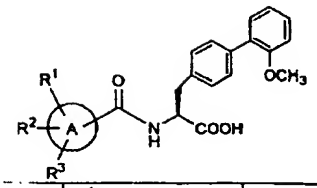
(0195)

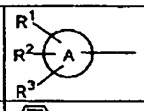
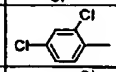
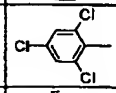
Table 2

Production Example	Chemical structural formula	m/z (MH+)
76		419
77		533
78		403
79		518
80		501
81		405 (M+)

(0196)

Table 3

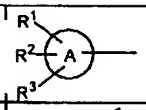
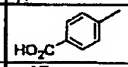
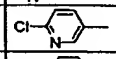
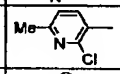
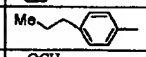
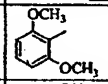
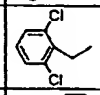
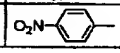


Production Example		m/z (MH+)
82		375
83		410
84		444
85		479
86		428
87		411
88		444
89		402
90		411

[0197]

(0197)

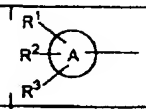
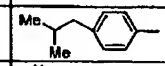
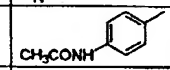
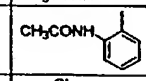
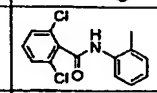
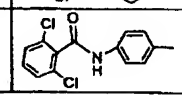
Table 4

Production Example		m/z (MH+)
91		419
92		444
93		411
94		425
95		403(M+)
96		464
97		417(M+)
98		435(M+)
99		405(M+)
99		458
101		420(M+)

[0198]

(0198)

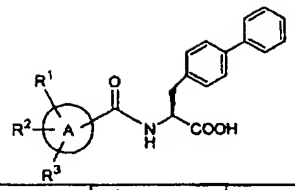
Table 5

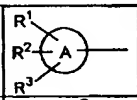
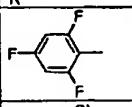
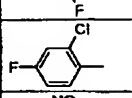
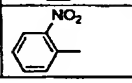
Production Example		m/z (MH+)
102		432
103		377(M+)
104		433
105		433
106		563
107		563

[0199]

(0199)

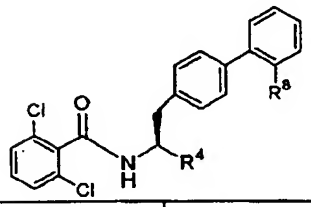
Table 6

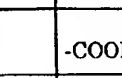
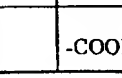


Production Example		m/z (MH+)
108		399
109		398
110		390(M+)

(0200)

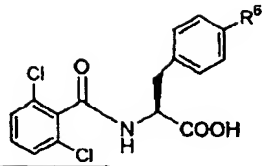
Table 7

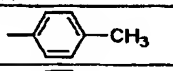
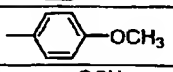
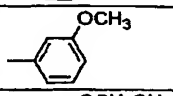
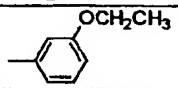
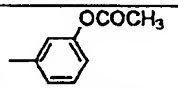
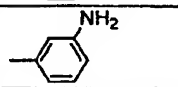
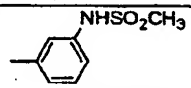
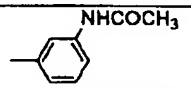
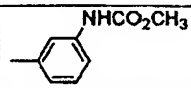
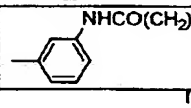


Production Example	R^8	R^4	m/z (MH+)
111	-H	-COOH	414
112	-Me	-COOH	428
113	$-CF_3$	-COOH	481
114	$-CH_2NHCH_2Ph$	-COOMe	547
115		-COOMe	534
116		-COOMe	534

(0201)

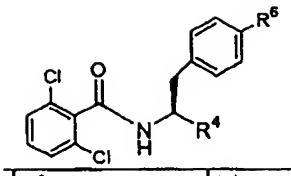
Table 8

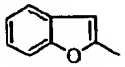


Production Example	R^6	m/z (MH$^+$)
117		428
118		444
119		444
120		458
121		456
122		429
123		507
124		471
125		487
126		527

(0202)

Table 9



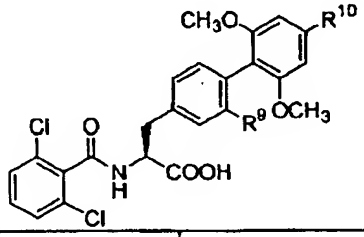
Production Example	R^6	R^4	m/z (MH+)
127		COOMe	429
128		COOH	420
129		COOH	415
130		COOH	454

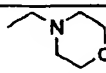
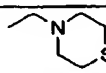
:]

【表１０】

(0203)

Table 10



Production Example	R^9	R^{10}	m/z (MH+)
131		H	518
132	H		559
133	H		573
134	H		589

1] 製造例１３５：Ｎ－（２，６－ジクロロベン　　ムロた：残渣をシリカゲルカラムクロマ

(0204)

Production Example 135

N-(2,6-dichlorobenzoyl)-4-(2,6-difluorophenyl)-L-phenylalanine

1) N-(2,6-dichlorobenzoyl)-O-(trifluoromethane sulfonyl)-L-tyrosine methyl ester was produced by process same as in description of Production Example 5-1) and 2).

2) $Pd(PPh_3)_4$ (0.34 g) was added under nitrogen to dioxane (30 ml) mixture of the product obtained as above (3.00 g), stannic hexamethyl (1.96 g) and anhydrous LiCl (0.76 g), and the

mixture was heated at 98°C for three hours. The mixture was cooled, diluted with ethyl acetate, filtered with celite, and evaporation was caused. Silica gel column chromatography (eluate, ethyl acetate / hexane (1 : 3)) purification was carried out on the residue, and N-(2,6-dichlorobenzoyl)-4-trimethyl stannio-L-phenylalanine methyl ester (2.46 g) was obtained.
ESMS: m/z 516 (MH+) and 514 (M-H)-.

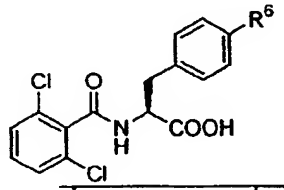
3) $Pd(PPh_3)_4$ (0.02 g) was added under nitrogen to the product obtained as above (0.17 g) and 1-bromo-2,6-difluorobenzene (95 mg) / toluene (2 ml) mixture, and the mixture was heated at 110°C for two hours. The mixture was evaporated. Silica gel column chromatography (eluate, ethyl acetate / hexane (1 : 3)) purification was carried out on the residue, and N-(2,6-dichlorobenzoyl)-4-(2,6-difluorophenyl)-L-phenylalanine methyl ester (58 mg) was obtained.
ESMS: m/z 464 (MH+), 486 (M++Na) and 562 (M-H)-.

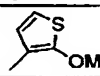
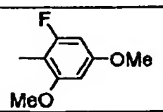
4) The product obtained as above (0.058 g) was hydrolysed using LiOH as described in Production Example 1-5) and the title compound (0.04 g) was obtained.
ESMS: m/z 450 (MH+), 472 (M++Na) and 448 (M-H)-.

The following compounds (Production Examples 136-140) were produced by a production method same as in description of Production Example 135 except that 1-bromo-2,6-difluorobenzene was replaced by necessary bromobenzene.

(0205)

Table 11



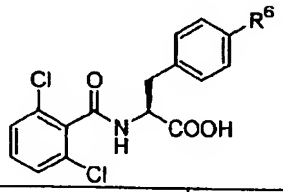
Production Example	R^6	MS, m/z
136		449 (M-H)⁻
137		415 (MH^+)
138		439 (MH^+)
139		492 (MH^+)
140		498 (MH^+)

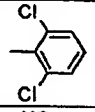
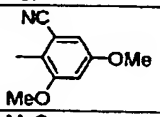
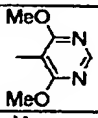
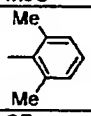
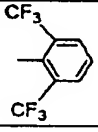
(0206)

The following compounds (Production Examples 141-146) were produced by a production method same as in description of Production Example 5 except that 2-methoxybenzene boronic acid was replaced by necessary benzene boronic acid.

(0207)

Table 12



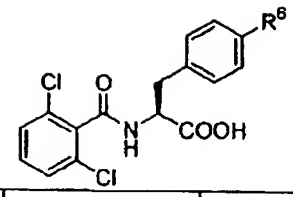
Production Example	R^6	MS: m/z	mp.°C
141		484 (MH^+)	
142		499(MH^+)	
143		460(MH^+)	
144		476(MH^+)	
145		442(MH^+)	200-201
146		550(MH^+)	259-260

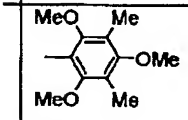
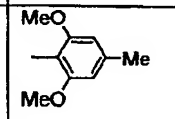
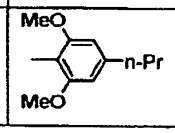
(0208)

The following compounds (Production Examples 147-149) were produced by process same as in description of Production Example 7 except that 1,3-dimethoxybenzene was replaced by necessary benzene.

(0209)

Table 13



Production Example	R^6	MS: m/z	mp.°C
147		532 (MH^+)	114-115
148		488 (MH^+)	233-234
149		516 (MH^+)	238-239 (分解)

(0210)

Production Example 150

N-(2,6-dichlorobenzoyl)-4-(2-cyano-6-carbamoyl phenyl)-L-phenylalanine.

1) N-(2,6-dichlorobenzoyl)-O-(trifluoromethane sulfonyl)-L-tyrosine methyl ester (0.5 g) was added under nitrogen to DME / water (10 mL / 0.5 mL) mixture of 2,6-dicyanobenzene boronic acid (0.516 g) and anhydrous potassium carbonate (0.52 g). $Pd(PPh_3)_4$ catalyst (0.1 g) was added, and the mixture was heated at 80°C for five hours. The mixture was cooled, diluted with ethyl acetate, and washed successively with water and aqueous sodium chloride. The organic layer was dried with magnesium sulfate and evaporated, and silica gel column chromatography (eluate, ethyl acetate / hexane (3 : 1)) purification was carried out on the residue, and N-(2,6-dichlorobenzoyl)-4-(2-cyano-6-carbamoyl phenyl)-L-phenylalanine methyl ester (325 mg) was obtained.
ESMS: m/z 496 (MH+), 494 (M-H)-.

2) The product obtained as above (150 mg) was hydrolysed using LiOH as described in Production Example 1-5) and the title compound (0.06 g) was obtained.
MS: m/z 465 (MH+).

(0211)

Production Example 151

N-(2,6-dichlorobenzoyl)-4-(2,6-dicyano phenyl)-L-phenylalanine.

1) N-(2,6-dichlorobenzoyl)-O-(trifluoromethane sulfonyl)-L-tyrosine methyl ester (0.5 g) was added under nitrogen to toluene (10 ml) mixture of 2,6-dicyanobenzene boronic acid (0.516 g) and anhydrous potassium carbonate (0.2 g). $Pd(PPh_3)_4$ (0.1 g) was added, and the mixture was heated at 90°C for eight hours. The mixture was cooled, diluted with ethyl acetate, and washed successively with water and aqueous sodium chloride. The organic layer was dried with magnesium sulfate and evaporated, and silica gel column chromatography (eluate, ethyl acetate / hexane (1 : 1)) purification was carried out on the residue, and N-(2,6-dichlorobenzoyl)-4-(2,6-dicyano phenyl)-L-phenylalanine methyl ester (58 mg) was obtained.

2) The product obtained as above was hydrolysed by a production method same as in description of Production Example 1-5) and the title compound was obtained.
MS: m/z 482 (MH+).

(0212)

Production Example 152

N-(2,6-dichlorobenzoyl)-4-[2-(methylsulfonyl) phenyl]-L-phenylalanine (152B) and N-(2,6-dichlorobenzoyl)-4-[2-(methylsulfinyl) phenyl]-L-phenylalanine (152A and 152C).

1) N-(2,6-dichlorobenzoyl)-4-[2-(methylthio) phenyl]-L-phenylalanine methyl ester (0.35 g) was dissolved in methylene chloride (5 ml). The mCPBA (0.255 g) was added at 0°C, and the mixture was stirred at 0°C for two hours. The mixture was washed successively with sodium bicarbonate aqueous solution, water and aqueous sodium chloride, dried with magnesium sulfate, filtered and evaporated. Silica gel column chromatography (eluate, ethyl acetate / hexane (1 : 3)) purification was carried out on the residue, and N-(2,6-dichlorobenzoyl)-4-[2-(methylsulfonyl) phenyl]-L-phenylalanine methyl ester (0.125 g, ESMS: m/z 506 (MH+), 528 (M++Na), 504 (M+-1)) and N-(2,6-dichlorobenzoyl)-4-[2-(methylsulfinyl) phenyl]-L-phenylalanine methyl ester (mixture of 2 diastereomers, 0.227 mg, ESMS: m/z 490 (MH+), 512 (M++Na), 488 (M-1)-) were obtained.

2) N-(2,6-dichlorobenzoyl)-4-[2-(methylsulfonyl) phenyl]-L-phenylalanine methyl ester was hydrolysed using LiOH as described in Production Example 1-5), and N-(2,6-dichlorobenzoyl)-4-[2-(methylsulfonyl) phenyl]-L-phenylalanine (152B) was obtained.
ESMS: m/z 492 (MH+), 514 (M++Na), 491 (M-H)-.

3) N-(2,6-dichlorobenzoyl)-4-[2-(methylsulfinyl) phenyl]-L-phenylalanine methyl ester (mixture of 2 diastereomers) was hydrolysed using LiOH as described in Production Example 1-5), and N-(2,6-dichlorobenzoyl)-4-[2-(methylsulfinyl) phenyl]-L-phenylalanine (mixture of 2 diastereomers) was obtained. The mixture was dissolved in methylene chloride, and a solid was

recovered by filtration, washed with methylene chloride and dried, and one of diastereomer of N-(2,6-dichlorobenzoyl)-4-[2-(methylsulfinyl) phenyl]-L-phenylalanine (152A) (80 mg) was obtained.

ESMS: m/z 476 (MH+), 498 (M++Na), 474 (M-H)-.

^{1}H-NMR (DMSO-d_6): δ 2.41 (s, 3H), 2.97 (m, 1H), 3.2 (dd, 1H), 4.72 (m, 1H), 7.32 (m, 3H), 7.4 (m, 5H), 7.6-7.7 (m, 2H), 8.0 (d, 1H), 9.15 (d, 1H).

The filtrate was evaporated, and the residue was crystallised (from ethyl acetate / hexane), and another diastereomer (152C) (44mg) of N-(2,6-dichlorobenzoyl)-4-[2-(methylsulfinyl) phenyl]-L-phenylalanine was obtained.

ESMS: m/z 476 (MH+), 498 (M++Na), 474 (M-H)-.

^{1}H-NMR (DMSO-d_6): δ 2.43 (s, 3H), 2.98 (m, 1H), 3.22 (m, 1H), 4.74 (m, 1H), 7.32 (m, 3H), 7.4 (m, 5H), 7.6-7.7 (m, 2H), 8.0 (d, 1H), 9.15 (d, 1H).

(0213)

Production Example 153

N-(2,6-dichlorobenzoyl)-4-(2,6-dimethoxy-3-fluorophenyl)-L-phenylalanine (153A) and N-(2,6-dichlorobenzoyl)-4-(2,6-dimethoxy-3,5-difluorophenyl)-L-phenylalanine (153B).

1) N-(2,6-dichlorobenzoyl)-4-(2,6-dimethoxyphenyl)-L-phenylalanine methyl ester (232 mg) was dissolved in anhydrous acetonitrile (10 ml) under nitrogen, and 3,5-dichloro-1-fluoro pyridinium trifluoromethanesulfonate (85 %, 353 mg) was added, and the mixture was refluxed for one day. Furthermore, 3,5-dichloro-1-fluoro pyridinium trifluoromethanesulfonate (175 mg) was added and the mixture was further refluxed for one day. Thereafter, mixture was concentrated, and the residue was dissolved in water, and extraction was carried out with methylene chloride. The liquid extract was washed with saturated sodium bicarbonate and water, dried with magnesium sulfate, filtered, and evaporation was caused. Silica gel preparative TLC (eluate, hexane / ethyl acetate (5 : 1- 2 : 1)) purification was carried out on the residue, and N-(2,6-dichlorobenzoyl)-4-(2,6-dimethoxy-3-fluorophenyl)-L-phenylalanine methyl ester (109 mg) and N-(2,6-dichlorobenzoyl)-4-(2,6-dimethoxy-3,5-difluorophenyl)-L-phenylalanine methyl ester (37 mg) were obtained.

2) Two products obtained as above were separately hydrolysed by process same as in description of Production Example 1-5), and N-(2,6-dichlorobenzoyl)-4-(2,6-dimethoxy-3-fluorophenyl)-L-phenylalanine (153A) (mp. 228-229°C, MS: m/z 492 (MH+)) and N-(2,6-dichlorobenzoyl)-4-(2,6-dimethoxy-3,5-difluorophenyl)-L-phenylalanine (153B) (mp. 201-202°C, MS: m/z 510 (MH+)) were obtained.

(0214)

Production Example 154

N-(2,6-dichlorobenzoyl)-4-(2,3-methylene dioxy-5-fluoro-6-methoxyphenyl)-L-phenylalanine.

The title compound was produced using the same procedures as in description of Production Example 153.

mp. 198-199°C.

(0215)

Production Example 155

N-(2,6-dichlorobenzoyl)-4-[4-(N-allyl-N-t-butoxycarbonyl amino)-2,6-dimethoxyphenyl]-L-phenylalanine.

1) 4-(N-allyl-N-t-butoxycarbonyl amino)-2,6-dimethoxybenzene boronic acid and N-(2,6-dichlorobenzoyl)-O-(trifluoromethane sulfonyl)-L-tyrosine methyl ester were subjected to a coupling reaction by process same as in description of Production Example 7-2), and N-(2,6-dichlorobenzoyl)-4-[4-(N-allyl-N-t-butoxycarbonyl amino)-2,6-dimethoxyphenyl]-L-phenylalanine methyl ester was obtained.

2) The product obtained as above was hydrolysed by process same as in description of Production Example 1-5), and the title compound was obtained.

mp. 138-139°C, MS: m/z 629 (MH+).

(0216)

Production Example 156

N-(2,6-dichlorobenzoyl)-4-(4-arylamino-2,6-dimethoxyphenyl)-L-phenylalanine.

1) N-(2,6-dichlorobenzoyl)-4-[4-[(N-allyl-N-t-butoxycarbonyl amino)-2,6-dimethoxyphenyl]-L-phenylalanine methyl ester (1.25 g) was dissolved in methylene chloride (10 ml), and TFA (10 ml) was added, and the mixture was stirred at room temperature under nitrogen for one hour 30 minutes. The mixture was evaporated, and the residue was dissolved in methylene chloride, washed with saturated sodium bicarbonate, dried with magnesium sulfate, filtered, and evaporation was caused. Silica gel column chromatography (eluate, hexane / ethyl acetate (5 : 1- 1 : 1)) purification was carried out on the residue, and N-(2,6-dichlorobenzoyl)-4-(4-arylamino-2,6-dimethoxyphenyl)-L-phenylalanine methyl ester (938 mg) was obtained.

2) The product obtained as above was hydrolysed by process same as in description of Production Example 1-5), and the title compound was obtained.

mp. 262-263°C (degradation), MS: m/z 529 (MH+).

(0217)

Production Example 157

N-(2,6-dichlorobenzoyl)-4-(4-amino-2,6-dimethoxyphenyl)-L-phenylalanine.

1) N-(2,6-dichlorobenzoyl)-4-(4-arylamino-2,6-dimethoxyphenyl)-L-phenylalanine methyl ester (0.93 g) was dissolved in acetonitrile / water (40 mL, 84 : 16) under nitrogen. Wilkinson catalyst (79 mg) was added, and the mixture was boiled. Two hours were allowed to pass, and catalyst (170 mg) was added furthermore, and the reaction was continued for further six hours. The solvent was evaporated, and remaining water was evaporated together with acetonitrile. Silica gel preparative TLC (eluate, hexane / ethyl acetate (2 : 1-1 : 2)) purification was carried out on the residue, and N-(2,6-dichlorobenzoyl)-4-(4-amino-2,6-dimethoxyphenyl)-L-phenylalanine methyl ester (708 mg) was obtained.

2) The product obtained as above was hydrolysed by process same as in description of Production Example 1-5), and the title compound was obtained.
mp. 221-222°C, MS: m/z 489 (MH+).

(0218)

Production Example 158

N-(2,6-dichlorobenzoyl)-4-(4-methoxycarbonylamino-2,6-dimethoxyphenyl)-L-phenylalanine.
By a production method same as in description of Production Example 64, the title compound was obtained by reacting N-(2,6-dichlorobenzoyl)-4-(4-amino-2,6-dimethoxyphenyl)-L-phenylalanine methyl ester and MeOCOCl instead of $MeSO_2Cl$.
mp. 235-236°C, MS: m/z 548 (MH+).

(0219)

Production Example 159

N-(2,6-dichlorobenzoyl)-4-(4-acetylamino-2,6-dimethoxyphenyl)-L-phenylalanine.
By a production method same as in description of Production Example 64, the title compound was obtained by reacting N-(2,6-dichlorobenzoyl)-4-(4-amino-2,6-dimethoxyphenyl)-L-phenylalanine methyl ester and MeCOCl instead of $MeSO_2Cl$.
mp. 243-244°C, MS: m/z 531 (MH+).

(0220)

Production Example 160

N-(2,6-dichlorobenzoyl)-4-[4-(3-methyl ureide)-2,6-dimethoxyphenyl]-L-phenylalanine.
By a production method same as in description of Production Example 70, the title compound

was obtained by reacting N-(2,6-dichlorobenzoyl)-4-(4-amino-2,6-dimethoxyphenyl)-L-phenylalanine methyl ester and MeNCO instead of MeNCS.

mp. 206-207°C, MS: m/z 547 (MH+).

(0221)

Production Example 161

N-(2,6-dichlorobenzoyl)-4-[4-[3-(2-methylphenyl) ureide]-2,6-dimethoxyphenyl]-L-phenylalanine.

By a production method same as in description of Production Example 70, the title compound was obtained by reacting N-(2,6-dichlorobenzoyl)-4-(4-amino-2,6-dimethoxyphenyl)-L-phenylalanine methyl ester and 2-methylphenyl isocyanate instead of MeNCS.

mp. 194-195°C, MS: m/z 622 (MH+).

(0222)

Production Example 162

N-(2,6-dichlorobenzoyl)-4-[2,6-dimethoxy-4-(3-methylthio ureide) phenyl]-L-phenylalanine.

The title compound was produced with starting from the N-(2,6-dichlorobenzoyl)-4-(2,6-dimethoxy-4-aminophenyl)-L-phenylalanine methyl ester by a production method same as in description of Production Example 70.

MS: m/z 562 (MH+), mp. 197-198°C.

(0223)

Production Example 163

N-(2,6-dichlorobenzoyl)-4-[2,6-dimethoxy-4-[(methylsulfonyl) amino] phenyl]-L-phenylalanine.

The title compound was thereby obtained with starting from the N-(2,6-dichlorobenzoyl)-4-(2,6-dimethoxy-4-aminophenyl)-L-phenylalanine methyl ester with form same as in description of Production Example 64.

MS: m/z 567 (MH+), mp. 154-155°C.

(0224)

Production Example 164

N-(2,6-dichlorobenzoyl)-4-[2,6-dimethoxy-4-(dimethylamino) phenyl]-L-phenylalanine.

The title compound was thereby obtained with form same as in description of Production Example 27, starting from the N-(2,6-dichlorobenzoyl)-4-(2,6-dimethoxy-4-aminophenyl)-L-phenylalanine methyl ester.

MS: m/z 517 (MH+).

(0225)

Production Example 165

N-(2,6-dichlorobenzoyl)-4-(4-methylcarbamoyl-2,6-dimethoxyphenyl)-L-phenylalanine.

1) 4-(1,3-dioxolan-2-yl)-2,6-dimethoxybenzene boronic acid was reacted with N-(2,6-dichlorobenzoyl)-O-(trifluoromethane sulfonyl)-L-tyrosine methyl ester using the same procedures as in description of Production Example 7-2), and N-(2,6-dichlorobenzoyl)-4-[4-(1,3-dioxolan-2-yl)-2,6-dimethoxyphenyl]-L-phenylalanine methyl ester was obtained.

2) The product obtained as above was dissolved in THF (60 ml), and 5 % hydrochloric acid (30 ml) was added to said solution. The mixture was stirred at room temperature under nitrogen for three hours. The mixture was evaporated, and water (50 ml) was added to the said residue. The mixture was extracted with methylene chloride, dried with magnesium sulfate, filtered, and evaporation was caused. Silica gel column chromatography (eluate, hexane / ethyl acetate (2 : 1-1 : 1)) purification was carried out on the residue, and N-(2,6-dichlorobenzoyl)-4-(4-formyl-2,6-dimethoxyphenyl)-L-phenylalanine methyl ester (2.06 g) was obtained.

3) The product obtained as above was oxidised by a production method same as in description of Production Example 52-1), and N-(2,6-dichlorobenzoyl)-4-(4-carboxy-2,6-dimethoxyphenyl)-L-phenylalanine methyl ester was obtained.

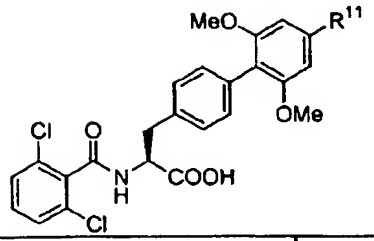
4) The product obtained as above was reacted with methylamine by a production method same as in description of Production Example 53, and the title compound was thereby obtained.
MS: m/z 531 (MH+), mp. 251-252°C.

(0226)

The following compounds (Production Examples 166-171) were produced using N-(2,6-dichlorobenzoyl)-4-(4-carboxy-2,6-dimethoxyphenyl)-L-phenylalanine methyl ester and suitable amine by a process same as in description of Production Example 53.

(0227)

Table 14



Production Example	R^{11}	m/z MH+	mp.°C
166	-$CONMe_2$	545	219-221
167	-CONHBn	607	153-154
168	-CONH-i-Pr	559	261-262
169	-$CONH(CH_2)_3OH$	575	222-223
170	-CO-N N-Me	614	234-235
171	-CONH N O	630	268-269

(0228)

Production Example 172

N-(2,6-dichlorobenzoyl)-4-(4-carboxy-2,6-dimethoxyphenyl)-L-phenylalanine

N-(2,6-dichlorobenzoyl)-4-(4-carboxy-2,6-dimethoxyphenyl)-L-phenylalanine methyl ester was hydrolysed by a production method same as in description of Production Example 1-5), and the title compound was obtained.

MS: m/z 517 (MH+), mp. 277-278°C.

(0229)

Production Example 173

N-(2,6-dichlorobenzoyl)-4-[4-(methanesulphonyl amino) carbonyl-2,6-dimethoxyphenyl]-L-phenylalanine.

By a production method same as in description of Production Example 61, the title compound was obtained using N-(2,6-dichlorobenzoyl)-4-(4-carboxy-2,6-dimethoxyphenyl)-L-phenylalanine methyl ester.

MS: m/z 595 (MH+), mp. 277-278°C.

(0230)

Production Example 174

N-(2,6-dichlorobenzoyl)-4-(2,6-dimethoxy-3-methoxymethoxy phenyl)-L-phenylalanine.

1) 2,6-dimethoxy-3-methoxymethoxy benzene boronic acid and N-(2,6-dichlorobenzoyl)-O-(trifluoromethane sulfonyl)-L-tyrosine methyl ester were subjected to a coupling reaction by process same as in description of Production Example 7-2), and N-(2,6-dichlorobenzoyl)-4-(2,6-dimethoxy-3-methoxymethoxy phenyl)-L-phenylalanine methyl ester was obtained.

2) The product obtained as above was hydrolysed according to a production method same as in description of Production Example 7-3), and the title compound was obtained.
MS: m/z 534 (MH+), mp. 156-157°C.

(0231)

Production Example 175

N-(2,6-dichlorobenzoyl)-4-(2,6-dimethoxy-3-hydroxyphenyl)-L-phenylalanine.

1) N-(2,6-dichlorobenzoyl)-4-(2,6-dimethoxy-3-methoxymethoxy phenyl)-L-phenylalanine methyl ester (165 mg) was dissolved in methanol (5 ml), and 4M dioxane solution (1 ml) of hydrochloric acid was added to said mixture. The mixture was stirred at room temperature for three hours. The mixture was evaporated, and the residue was dissolved in water (40 ml) and extraction was carried out with methylene chloride. The liquid extract was dried with magnesium sulfate, filtered, and evaporation was caused. Silica gel preparative TLC (eluate, hexane / ethyl acetate (3 : 1-1: 1)) purification was carried out on the residue, and N-(2,6-dichlorobenzoyl)-4-(2,6-dimethoxy-3-hydroxyphenyl)-L-phenylalanine methyl ester (145 mg) was obtained.

2) The product obtained as above was hydrolysed by a production method same as in description of Production Example 1-5), and the title compound was obtained.
mp. 164-165°C, MS: m/z 490 (MH+).

(0232)

Production Example 176

N-[2-chloro-4-(t-butoxycarbonyl) benzoyl]-4-(2-methoxyphenyl)-L-phenylalanine.

1) 2-chloro-4-(t-butoxycarbonyl) benzoic acid was subjected to a coupling reaction using a production method same as in description of Production Example 2-1) with release amine derived from 4-(2-methoxyphenyl)-L-phenylalanine methyl ester (Production Examples 1-3), and N-[2-chloro-4-(t-butoxycarbonyl) benzoyl]-4-(2-methoxyphenyl)-L-phenylalanine methyl ester (0.332 g) was obtained.

3) The product obtained as above (19.8 mg) was hydrolysed by a process same as in description of Production Example 1-5), and the title compound (17.5 mg) was obtained.

MS: (m/z) 508 (M-H)-.

(0233)

Production Example 177

N-[2-chloro-4-carboxy benzoyl]-4-(2-methoxyphenyl)-L-phenylalanine.

1) N-[2-chloro-4-(t-butoxycarbonyl) benzoyl]-4-(2-methoxyphenyl)-L-phenylalanine methyl ester (305 mg) was dissolved in anhydrous methylene chloride (2 ml) under nitrogen, and TFA (2 ml) was added. The mixture was stirred at room temperature for two hours, and N-[2-chloro-4-carboxy benzoyl]-4-(2-methoxyphenyl)-L-phenylalanine methyl ester (315 mg) was obtained.

2) Thereafter, the product obtained as above (48.6 mg) was hydrolysed by a production method same as in description of Production Example 1-5), and N-[2-chloro-4-carboxy benzoyl]-4-(2-methoxyphenyl)-L-phenylalanine (42.9 mg) was obtained.
MS: (m/z) 452 (M-H)-.

(0234)

Production Example 178

N-[2-chloro-4-carbamoyl benzoyl]-4-(2-methoxyphenyl)-L-phenylalanine.
The title compound was produced using a production method same as in description of Production Example 60 from N-[2-chloro-4-carboxy benzoyl]-4-(2-methoxyphenyl)-L-phenylalanine methyl ester.
MS: (m/z) 451 (M-H)-.

(0235)

Production Example 179

N-[2-chloro-4-[N-(methanesulphonyl) carbamoyl]-benzoyl]-4-(2-methoxyphenyl)-L-phenylalanine.
The title compound was produced using a production method same as in description of Production Example 61 from N-[2-chloro-4-carboxy benzoyl]-4-(2-methoxyphenyl)-L-phenylalanine methyl ester.
MS: (m/z) 529 (M-H)-.

(0236)

Production Example 180

N-[2-chloro-5-[(trifluoromethane sulfonyl) amino] benzoyl]-4-(2-methoxyphenyl)-L-phenylalanine.
The title compound was produced by production methods same as in description of Production

Example 62, 63, 64 and 65 except that 2-chloro-4-nitrobenzoyl chloride in a coupling step of Production Example 62 was replaced by 2-chloro-5-nitrobenzoyl chloride.

MS: (m/z) 555 (M-H)-.

(0237)

Production Example 181

N-[2-chloro-3-[(trifluoromethane sulfonyl) amino] benzoyl]-4-(2-methoxyphenyl)-L-phenylalanine.

The title compound was produced by production methods same as in description of Production Example 62, 63, 64 and 65 except that 2-chloro-4-nitrobenzoyl chloride in a coupling step of Production Example 62 was replaced by 2-chloro-3-nitrobenzoyl chloride.

MS: (m/z) 555 (M-H)-.

(0238)

Production Example 182

N-[2,6-dichloro-4-[(trifluoromethane sulfonyl) amino] benzoyl]-4-(2-methoxyphenyl)-L-phenylalanine.

The title compound was obtained by continuously carrying out production method same as in description of Production Example 62, 63, 64 and 65 except using 2,6-dichloro-4-nitrobenzoic acid (US Patent No 3,423,475) during coupling step of Production Example 62.

MS: (m/z) 589 (M-H)-.

(0239)

Production Example 183

N-[2-chloro-4-[(trifluoromethane sulfonyl) amino] benzoyl]-4-(2,6-dimethoxyphenyl)-L-phenylalanine.

The title compound was obtained by continuously carrying out production method same as in description of Production Example 62, 63, 64 and 65 except that 4-(2-methoxyphenyl)-L-phenylalanine methyl ester was replaced by 4-(2,6-dimethoxyphenyl)-L-phenylalanine methyl ester.

MS: (m/z) 585 (M-H)-.

(0240)

Production Example 184

N-[2,6-dichloro-4-[(trifluoromethane sulfonyl) amino] benzoyl]-4-(2,6-dimethoxyphenyl)-L-phenylalanine.

The title compound was obtained by continuously carrying out production method same as in description of Production Example 62, 63, 64 and 65 except that 2,6-dichlorobenzoyl chloride

was replaced by 2,6-dichloro-4-nitrobenzoyl chloride, and 4-(2-methoxyphenyl)-L-phenylalanine methyl ester was replaced by 4-(2,6-dimethoxyphenyl)-L-phenylalanine methyl ester.

MS: (m/z) 619 (M-H)-.

(0241)

Production Example 185

N-[2-chloro-6-[(trifluoromethane sulfonyl) amino] benzoyl]-4-(2-methoxyphenyl)-L-phenylalanine.

The title compound was produced by production methods same as in description of Production Example 62, 63, 64 and 65 except using 2-amino-6-chlorobenzoic acid.

MS: (m/z) 555 (M-H)-.

(0242)

Production Example 186

N-[2-chloro-3-[(trifluoromethane sulfonyl) amino] benzoyl]-4-(2-methoxyphenyl)-D-phenylalanine.

Starting from the 4-(2-methoxyphenyl)-D-phenylalanine methyl ester, the title compound was obtained by a production method same as in description of Production Example 62, 63, 64 and 65.

MS: (m/z) 555 (M-H)-.

(0243)

The following compounds (Production Examples 187-193) were produced by production method same as in description of Production Example 62, 63, 64 and 65 except that MeSO2Cl was replaced by necessary aryl chloride sulfonyl.

(0244)

Production Example 187

N-[2-chloro-4-[[(4-trifluoromethylphenyl) sulfonyl] amino] benzoyl]-4-(2-methoxyphenyl)-L-phenylalanine.

ESMS: m/z 655 (M++Na), 633 (MH+), 631 (M-H)-.

(0245)

Production Example 188

N-[2-chloro-4-(tosyl amino) benzoyl]-4-(2-methoxyphenyl)-L-phenylalanine.

ESMS: m/z 601 (M++Na), 579 (MH+), 577 (M-H)-.

(0246)

Production Example 189

N-[2-chloro-4-[[(4-fluorophenyl) sulfonyl] amino] benzoyl]-4-(2-methoxyphenyl)-L-phenylalanine.

ESMS: m/z 605 (M++Na), 583 (MH+), 581 (M-H)-.

(0247)

Production Example 190

N-[2-chloro-4-[[(4-methoxyphenyl) sulfonyl] amino] benzoyl]-4-(2-methoxyphenyl)-L-phenylalanine.

ESMS: m/z 617 (M++Na), 595 (MH+), 593 (M-H)-.

(0248)

Production Example 191

N-[2-chloro-4-[(2-thienyl sulfonyl) amino] benzoyl]-4-(2-methoxyphenyl)-L-phenylalanine.

ESMS: m/z 593 (M++Na), 571 (MH+), 569 (M-H)-.

(0249)

Production Example 192

N-[2-chloro-4-[[(2-methylphenyl) sulfonyl] amino] benzoyl]-4-(2-methoxyphenyl)-L-phenylalanine.

ESMS: m/z 601 (M++Na), 579 (MH+), 577 (M-H)-.

(0250)

Production Example 193

N-[2,6-dichloro-4-[(2-thienyl sulfonyl) amino] benzoyl]-4-(2,6-dimethoxyphenyl)-L-phenylalanine

mp. 141-142°C. ESMS: m/z 635 (MH+).

(0251)

Production Example 194

N-[4-(3-benzylthio ureide)-2-chlorobenzoyl]-4-(2-methoxyphenyl)-L-phenylalanine.

1) DMF (1.5 ml) solution of N-(4-amino-2-chlorobenzoyl)-4-(2-methoxyphenyl)-L-phenylalanine (57 mg) was added to 1,1'-thiocarbonyl diimidazole (28 mg) dissolved in DMF (1 ml) at 0°C under nitrogen over a period of two hours 30 minutes. Thereafter, mixture was slowly warmed to room temperature and stirred for further two hours. Benzylamine (21 μL) was added, and the produced mixture was stirred at 80°C for two hours. The mixture was concentrated, and

the residue was dissolved in methylene chloride and was washed with 1N hydrochloric acid and water. The organic layer was dried with magnesium sulfate, filtered, and evaporation was caused. Silica gel preparative TLC (eluate, methylene chloride / methanol / Et_3N (100 : 1 : 1)) purification was carried out on the residue, and a solid was obtained. The said solid was dissolved in methylene chloride, washed with 1N hydrochloric acid, dried, and evaporation was caused, and N-[4-(3-benzylthio ureide)-2-chlorobenzoyl]-4-(2-methoxyphenyl)-L-phenylalanine methyl ester (42 mg) was obtained.

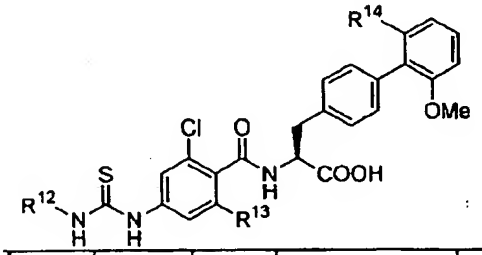
2) The product obtained as above was hydrolysed by a production method same as in description of Production Example 1-5), and the title compound (26.9 mg) was obtained.
ESMS: m / z 572 (M+-1).

(0252)

The following compounds (Production Examples 195-198) were produced with a form same as description of Production Example 70 except that methylisothiocyanate was replaced by suitable isothiocyanate compound.

(0253)

Table 15



Production Example	R^{12}	R^{13}	R^{14}	MS: m/z	mp.°C
195	i-Pr	H	H	524 $(M-H)^-$	
196	Et	H	H	510 $(M-H)^-$	155-156
197	Ph	H	H	558 $(M-H)^-$	145-146
198	Me	Cl	-OMe	546 $(M-OH)^+$	189-190

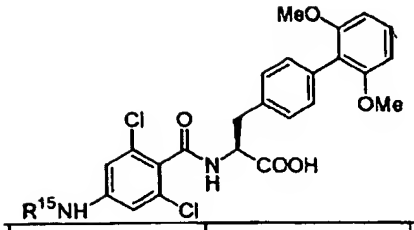
[41] 以下の化合物(製造例199～204)を [0255]

(0254)

The following compounds (Production Examples 199-204) were produced with form same as in description of Production Example 64, 69 or 70.

(0255)

Table 16



Production Example	R^{15}	m/z MH+	mp.°C
199	Ac	531	227-229
200	EtOCO	561	185-187
201	MeOCO	547	147-149
202	2-MeC_6H_4NHCO	622	182-184
203	MeNHCO	546	110-112
204	H_2NCO	532	220-221

(0256)

Production Example 205

N-(4-ureide-2,6-dichlorobenzoyl-4-(3-carbamoyl-2,6-dimethoxyphenyl)-L-phenylalanine.

The title compound was produced using a production method same as in description of Production Example 69.

ESMS: m/z 575 (MH+). mp. 217-219°C.

(0257)

Production Example 206

N-(4-amino-2,6-dichlorobenzoyl)-4-(2,6-dimethoxyphenyl)-L-phenylalanine.

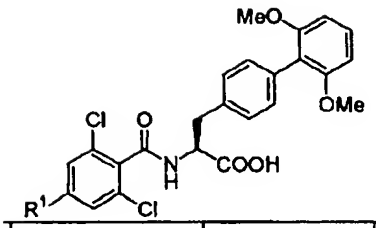
The title compound was produced using the same procedures as in description of Production Example 63.

ESMS: m/z 489 (MH+). mp. 221-222°C (degradation).

The following compounds (Production Examples 207-208) were produced by process same as in description of Production Example 2.

(0258)

Table 17



Production Example	R¹	m/z MH⁺	mp.°C
207	Br	554	184-185
208	OH	490	252-253

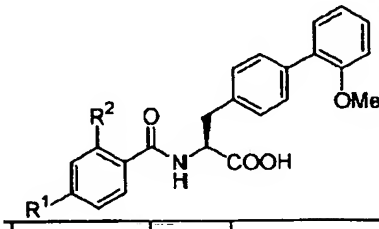
91 塩化2，6－ジクロロベンゾイルおよび　　2-12)を製造した。

(0259)

The following compounds (Production Examples 209-212) were produced with form same as in description of Production Example 1 and 2 except that 2,6-dichlorobenzoyl chloride and (S)-2-phenylpropionic acid were replaced by necessary benzoyl chloride and benzoic acid.

(0260)

Table 18



Production Example	R¹	R²	m/z MH⁺	mp.°C
209	OH	Cl	426	
210	H_2NSO_2	H	455	
211	$MeSO_2$	Cl	488	
212	Br	Cl	490	62-63

製造例213：N－[2－(2，6－ジクロロ　　法，実施例1で2－(2，6－ジクロロフェニル)

(0261)

Production Example 213

N-[2-(2,6-dichlorophenyl) propionyl]-4-(2-methoxyphenyl)-L-phenylalanine.

1) (2,6-dichlorophenyl) acetic acid (2.55 g) was dissolved in anhydrous methanol (60 ml), and HCl (gas) was aerated to said mixture, and the produced solution was stirred at room temperature for 18 hours. Thereafter, solvent was evaporated, and (2,6-dichlorophenyl) acetic acid methyl ester (2.7g) was obtained.

2) LDA (2M heptane / THF / ethyl benzene solution) was added to anhydrous THF (10 ml), and the mixture was cooled to -78°C under nitrogen. The product obtained as above (1.1 g) was added dropwise, and the mixture was stirred at -78°C for 30 minutes. MeI (0.467 ml) was added, and the mixture was warmed to room temperature, and it was stirred overnight. The mixture was concentrated. The residue was dissolved with ethyl acetate (75 ml) and washed successively with 1N hydrochloric acid, water and aqueous sodium chloride. The mixture was dried with magnesium sulfate, filtered, and evaporation was caused, and 2-(2,6-dichlorophenyl) propionic acid methyl ester (1.11 g) was obtained.

3) The product obtained as above was dissolved in THF / methanol / toluene (65 mL, 11 : 1 : 1) and 1M KOH (9.18 ml) was added. The mixture was stirred at room temperature for six hours and was heated to 50°C, and it was stirred overnight. Ethanol (5 ml) was added, and the mixture was stirred at 60°C for six hours, and it was refluxed overnight. The mixture was concentrated, dissolved with water (60 ml), and acidified to pH<2 with 1N hydrochloric acid. Product was recovered by filtration,, and 2-(2,6-dichlorophenyl) propionic acid (0.84 g) was obtained.

4) The product obtained as above was subjected to a coupling reaction with 4-(2-methoxyphenyl)-L-phenylalanine methyl ester by a production method same as in description of Production Example 2, and it was hydrolysed using LiOH, and the title compound was thereby obtained.
ESMS: m/z 472 (MH+). mp. 109-110°C.

The following compounds (Production Examples 214-217) were produced by a production method same as in description of Production Example 4.

(0262)

Production Example 214

N-(2,6-dichlorobenzoyl)-4-(2-formyl-3-thienyl)-L-phenylalanine

ESMS: m/z 470 (M++Na), 448 (MH+), 446 (M-H)-.

(0263)

Production Example 215

N-(2,6-dichlorobenzoyl)-4-(5-acetyl-2-thienyl)-L-phenylalanine

ESMS: m/z 484 (M++Na), 462 (MH+), 460 (M-H)-, mp. 194-195°C.

(0264)

Production Example 216

N-(2,6-dichlorobenzoyl)-4-[(3,5-dimethyl-4-isoxazolyl)-2,6-dimethoxyphenyl]-L-phenylalanine

ESMS: m/z 433 (MH+), mp. 118.7°C.

(0265)

Production Example 217

N-(2,6-dichlorobenzoyl)-4-(4-pyridyl)-L-phenylalanine

ESMS: m/z 415 (MH+).

(0266)

Production Example 218

N-(2,6-dichlorobenzoyl)-4-(2-hydroxymethyl-3-thienyl)-L-phenylalanine

N-(2,6-dichlorobenzoyl)-4-(2-formyl-3-thienyl)-L-phenylalanine methyl ester was reduced with $NaBH_4$, and continuingly hydrolysed in accordance with Production Example 50, and thereby the title compound was produced.

ESMS: m / z 472 (M++Na), 448 (M-H)-.

(0267)

Production Example 219

N-(2,6-dichlorobenzoyl)-4-(2-cyano-3-thienyl)-L-phenylalanine.

1) Dioxane (8 ml) mixture of N-(2,6-dichlorobenzoyl)-O-(trifluoromethane sulfonyl)-L-tyrosine methyl ester (361 mg), trimethyl (2-cyano-3-thienyl) tin (393 mg), $Pd(PPh_3)_4$ (42 mg) and LiCl (93 mg) was stirred at 100°C under nitrogen for 38 hours. The mixture was diluted with ethyl acetate, and treated with 10 % NH_4Cl aqueous solution (6 ml). After stirring at room temperature for one hour, mixture was filtered with celite and was washed with ethyl acetate. The organic layers were combined, washed successively with water and aqueous sodium chloride, dried with magnesium sulphate, and it was evaporated under reduced pressure. Silica gel chromatography purification was carried out on the residue, and N-(2,6-dichlorobenzoyl)-4-(2-cyano-3-thienyl)-L-phenylalanine methyl ester (126 mg) was obtained.

ESMS: m/z 481 (M++Na), 459 (MH+), 457 (M-H)-.

2) The product obtained as above was hydrolysed with LiOH as described in Production Example 1-5), and N-(2,6-dichlorobenzoyl)-4-(2-cyano-3-thienyl)-L-phenylalanine (110 mg) was obtained.

ESMS: m/z 467 (M++Na), 445 (MH+), 443 (M-H)-.

The following compounds (Production Examples 220-226) were produced with form same as in description of Production Example 32.

(0268)

Production Example 220

N-(2,6-dichlorobenzoyl)-4-[2,6-dimethoxy-4-(3-thienyl methoxy) phenyl]-L-phenylalanine.

ESMS: m/z 584 (M-H)-.

(0269)

Production Example 221

N-(2,6-dichlorobenzoyl)-4-[2,6-dimethoxy-4-[(2,6-dichlorophenyl) methoxy] phenyl]-L-phenylalanine.

ESMS: m/z 672 (M++Na), 648 (M-H)-.

(0270)

Production Example 222

N-(2,6-dichlorobenzoyl)-4-[2,6-dimethoxy-4-(2-hydroxyethoxy) phenyl]-L-phenylalanine.

ESMS: m/z 556 (M++Na), 534 (MH+), 532 (M-H)-.

(0271)

Production Example 223

N-(2,6-dichlorobenzoyl)-4-[2,6-dimethoxy-4-[2-(N,N-dimethylamino) ethoxy] phenyl]-L-phenylalanine.

ESMS: m/z 561 (MH)+.

(0272)

Production Example 224

N-(2,6-dichlorobenzoyl)-4-(3-isopropoxy phenyl)-L-phenylalanine.

ESMS: m/z 494 (M++Na), 472 (MH+), 470 (M-H)-.

(0273)

Production Example 225

N-(2,6-dichlorobenzoyl)-4-(2-isopropoxy phenyl)-L-phenylalanine.

ESMS: m/z 494 (M++Na), 472 (MH+), 470 (M-H)-.

(0274)

Production Example 226

N-(2,6-dichlorobenzoyl)-4-(2-isopropyl oxy-6-methoxyphenyl)-L-phenylalanine.

ESMS: m/z 524 (M++Na), 500 (M-H)-.

(0275)

Production Example 227

N-(2,6-dichlorobenzoyl)-4-[6-methoxy-2-(2-hydroxyethoxy) phenyl]-L-phenylalanine.

1) 6-methoxy-2-methoxymethoxy benzene boronic acid (1.92 g) was subjected to a coupling reaction with N-(2,6-dichlorobenzoyl)-O-(trifluoromethane sulfonyl)-L-tyrosine ethyl ester by a production method same as in Production Example 5-3), and N-(2,6-dichlorobenzoyl)-4-(6-methoxy-2-methoxymethoxy phenyl)-L-phenylalanine ethyl ester (0.942 mg) was obtained.
ESMS: m/z 532 (MH+), 530 (M-H)-.

2) To N-(2,6-dichlorobenzoyl)-4-(6-methoxy-2-methoxymethoxy phenyl)-L-phenylalanine ethyl ester (938 mg) dissolved in ethanol (25 ml) was added hydrochloric acid (4N dioxane solution, 5 mL), and thereafter, mixture was stirred at room temperature under nitrogen for four hours. The mixture was diluted with ethyl acetate, washed with water and aqueous sodium chloride, dried with magnesium sulfate, and evaporation was caused. Silica gel column chromatography (eluate, ethyl acetate / hexane (1 : 2)) purification was carried out on the residue, and N-(2,6-dichlorobenzoyl)-4-(6-methoxy-2-hydroxyphenyl)-L-phenylalanine ethyl ester (795 mg) was obtained.
ESMS: m/z 488 (MH+), 486 (M-H)-.

3) DMF (5 ml) mixture of product obtained as above (256 mg), 2-bromoethyl acetate (271 mg) and potassium carbonate (217 mg) was stirred at 60°C under nitrogen for 15 hours. The mixture was diluted with ethyl acetate, washed with water and aqueous sodium chloride, dried with magnesium sulfate, and evaporation was caused. Silica gel column chromatography (eluate, ethyl acetate / hexane(1 : 5-1 : 3)) purification was carried out on the residue, and N-(2,6-dichlorobenzoyl)-4-[6-methoxy-2-(2-acetoxy ethoxy) phenyl]-L-phenylalanine ethyl ester (203 mg) was obtained.
ESMS: m/z 574 (MH+), 572 (M-H)-.

4) The product obtained as above (196 mg) was hydrolysed using LiOH (29 mg) as described in Production Example 1-5). Crude substance was crystallised from the methylene chloride / ethyl acetate / hexane, and the title compound (145 mg) was obtained.
mp. 158-159°C. ESMS: m/z 526 (M++Na), 504 (MH+), 502 (M-H)-.

(0276)

Production Example 228

N-(2,6-dichlorobenzoyl)-4-[6-methoxy-2-(2-fluoro ethoxy) phenyl]-L-phenylalanine.

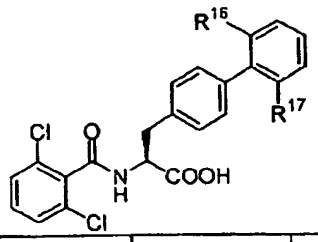
The title compound was produced by same process as in Production Example 227 except that 2-bromoethyl acetate was replaced by 2-fluoroethyl bromide.

mp. 206-207°C. ESMS: m/z 506 (MH+).

The following compounds (Production Examples 229-232) were produced using necessary benzene boronic acid by a production method same as in description of Production Example 227.

(0277)

Table 19



Production Example	R^{16}	R^{17}	m/z (MH^+)	mp.°C
229	$-OCH_2CH_2OH$	$-OCH_2CH_2OH$	534	124-125
230	$-OCH_2CF_3$	$-OCH_2CF_3$	610	93-94
231	$-OCH_2CN$	$-OCH_2CN$	524	175-176
232	$-OCH_2CH_2N(CH_3)_2$	-OH	517	168-169

8] 以下の化合物(製造例233～241)を、ESMS：m/z 518 (MH^+)，516 ($M-H)^-$。

(0278)

The following compounds (Production Examples 233-241) were produced using necessary benzene boronic acid by a production method same as in description of Production Example 228.

(0279)

Production Example 233

N-(2,6-dichlorobenzoyl)-4-[2,3-methylene dioxy-6-(2-methoxyethoxy) phenyl]-L-phenylalanine

mp. 167-168°C. ESMS: m/z 532 (MH+).

(0280)

Production Example 234

N-(2,6-dichlorobenzoyl)-4-[2,3-methylene dioxy-6-[2-(N,N-dimethylamino) ethoxy] phenyl]-L-phenylalanine

ESMS: m/z 545 (MH+), 543 (M-H)-.

(0281)

Production Example 235

N-(2,6-dichlorobenzoyl)-4-[2,3-methylene dioxy-6-(methoxymethoxy) phenyl]-L-phenylalanine

ESMS: m/z 518 (MH+), 516 (M-H)-.

(0282)

Production Example 236

N-(2,6-dichlorobenzoyl)-4-(2,3-methylene dioxy-6-hydroxyphenyl)-L-phenylalanine

ESMS: m/z 474 (MH+).

(0283)

Production Example 237

N-(2,6-dichlorobenzoyl)-4-(2,3-methylene dioxy-6-ethoxyphenyl)-L-phenylalanine

ESMS: m/z 502 (MH+).

(0284)

Production Example 238

N-(2,6-dichlorobenzoyl)-4-[2,3-methylene dioxy-6-(2-hydroxyethoxy) phenyl]-L-phenylalanine

ESMS: m/z 518 (MH+), 516 (M-H)-.

(0285)

Production Example 239

N-(2,6-dichlorobenzoyl)-4-[2,3-methylene dioxy-6-(cyano methoxy) phenyl]-L-phenylalanine

ESMS: m/z 513 (MH+).

(0286)

Production Example 240

N-(2,6-dichlorobenzoyl)-4-(2,3-methylene dioxy-6-methoxyphenyl)-L-phenylalanine

ESMS: m/z 488 (MH+).

(0287)

Production Example 241

N-(2,6-dichlorobenzoyl)-4-(2,3-ethylenedioxy-6-methoxyphenyl)-L-phenylalanine

ESMS: m/z 502 (MH+), mp. 218°C.

(0288)

Production Example 242

N-(2,6-dichlorobenzoyl)-4-[2,6-dimethoxy-4-[(methylamino) methyl] phenyl]-L-phenylalanine

1) DME / water (20 mL / 0.5 mL) mixture of 2,6-dimethoxy-4-[(t-butyl diphenyl silyloxy) methyl] benzene boronic acid (5.2 g), N-(2,6-dichlorobenzoyl)-4-bromo-L-phenylalanine ethyl

ester (1.71 g), $Pd(PPh_3)_4$ (0.44 g) and potassium carbonate (1.59 g) was heated at 80°C under nitrogen for 24 hours. The mixture was worked up and refined by a production method same as in Production Example 8-3), and N-(2,6-dichlorobenzoyl)-4-[2,6-dimethoxy-4-[(t-butyl diphenyl silyloxy) methyl] phenyl]-L-phenylalanine ethyl ester (2.9 g) was obtained.
ESMS: m/z 770 (MH+).

2) To ice cooled solution of THF (10 ml) of the product obtained as above (2.9 g) was added tetrabutyl ammonium fluoride under nitrogen (4.45 mL, 1M THF solution), and the mixture was stirred for two hours. THF was evaporated, and preparative TLC (eluate, hexane-50 % hexane / ethyl acetate) purification was carried out on the residue, and N-(2,6-dichlorobenzoyl)-4-[2,6-dimethoxy-4-(hydroxymethyl) phenyl]-L-phenylalanine ethyl ester (1.86 g) was obtained.
ESMS: m/z 532 (MH+).

3) Methylene chloride (20 ml) mixture of the product obtained as above (1.8 g), CBr_4 (2.25 g) and Ph_3P (1.78 g) was stirred overnight at 0°C. The solvent was evaporated, and silica gel column chromatography (eluate, hexane-10 % hexane / ethyl acetate) purification was carried out on the residue, and N-(2,6-dichlorobenzoyl)-4-[2,6-dimethoxy-4-(bromomethyl) phenyl]-L-phenylalanine ethyl ester (0.9 g) was obtained.
ESMS: m/z 596 (MH+).

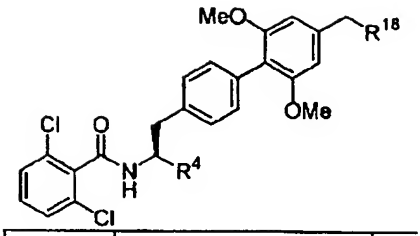
4) Methylene chloride (3 ml) mixture of the product obtained as above (0.15 g) and $MeNH_2$ (2M THF solution, 0.8 mL) was stirred at room temperature for four hours. Silica gel preparative TLC (eluate, methylene chloride / ethanol [9.5 : 5], combined with several drops of NH_4OH) purification was carried out with crude mixture, and N-(2,6-dichlorobenzoyl)-4-[2,6-dimethoxy-4-[(methylamino) methyl] phenyl]-L-phenylalanine ethyl ester (45 mg) was obtained.
ESMS: m/z 545 (MH+).

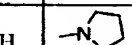
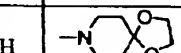
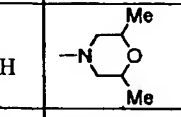
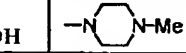
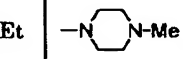
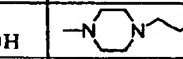
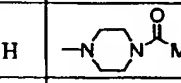
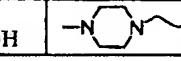
5) The product obtained as above (0.093 g) was hydrolysed using LiOH (2N solution, 0.175 mL) in accordance with Production Example 1-5), and the title compound (75 mg) was obtained.
mp. 274°C. ESMS: m/z 517 (MH+).

The following compounds (Production Examples 243-252) were produced with similar form as described in Production Example 242 except that $MeNH_2$ was replaced by necessary amine.

(0289)

Table 20



Production Example	R4	R18	Physical constant
243	-COOH		MS: m/z 557 (MH^+)
244	-COOH		MS: m/z 629 (MH^+)
245	-COOH		MS: m/z 601 (MH^+)
246	-COOH	$-NH(CH_2)_2OH$	MS: m/z 547 (MH^+)
247	-COOH	$-N(Me)CH_2CH_2N(Me)_2$	MS: m/z 588 (MH^+)
248	-COOH		MS: m/z 586 (MH^+)
249	-COOEt		MS: 614 (MH^+) mp. 148-150.5°C dihydro chloride: mp. 235°C (degradation)
250	-COOH		MS: m/z 616 (MH^+)
251	-COOH		MS: m/z 614 (MH^+)
252	-COOH		MS: m/z 614 (MH^+)

(0290)

Production Example 253

N-(2,6-dichlorobenzoyl)-4-[2,6-dimethoxy-4-(thiomorpholinomethyl) phenyl]-L-phenylalanine.

1) DME / water (10 mL / 0.5 mL) mixture of 2,6-dimethoxy-4-(thiomorpholinomethyl) benzene boronic acid (1.1 g), N-(2,6-dichlorobenzoyl)-4-bromo-L-phenylalanine ethyl ester (0.71 g), $Pd(PPh_3)_4$ (1.0 g) and potassium carbonate (1.00 g) was heated at 80°C under nitrogen for six hours. The mixture was worked up, and purification was carried out according to a production method of description in Production Example 8-3), and N-(2,6-dichlorobenzoyl)-4-[2,6-dimethoxy-4-(thiomorpholinomethyl) phenyl]-L-phenylalanine ethyl ester (0.15 g) was obtained.

mp. 86-89°C. ESMS: m/z 616 (MH+), hydrochloride: mp. 204-205°C.

2) The product obtained as above (0.15 g) was hydrolysed using LiOH as described in Production

Example 1-5), and the title compound (120 mg) was obtained.
ESMS: m/z 588 (MH+).

The following compounds (Production Examples 254-261) were produced from the necessary starting material with a form same as in description of Production Example 242 or 253.

(0291)

Production Example 254

N-(2,6-dichlorobenzoyl)-4-[2,6-dimethoxy-4-[(diethylamino) methyl] phenyl]-L-phenylalanine.
ESMS: m/z 559 (MH+).

(0292)

Production Example 255

N-(2,6-dichlorobenzoyl)-4-[2,6-dimethoxy-4-[(N,N-dimethylamino) methyl] phenyl]-L-phenylalanine.
ESMS: m/z 531 (MH+).

(0293)

Production Example 256

N-(2,6-dichlorobenzoyl)-4-[2,6-dimethoxy-4-(piperidinomethyl) phenyl]-L-phenylalanine.
ESMS: m/z 571 (MH+).

(0294)

Production Example 257

N-(2,6-dichlorobenzoyl)-4-[2,6-dimethoxy-4-(morpholinomethyl) phenyl]-L-phenylalanine
ESMS: m/z 573 (MH+).

Production Example 258

N-(2,6-dichlorobenzoyl)-4-[2,6-dimethoxy-4-[(4-benzyl-1-piperazinyl) methyl] phenyl]-L-phenylalanine
ESMS: m/z 662 (MH+).

(0295)

Production Example 259

N-(2,6-dichlorobenzoyl)-4-[2,6-dimethoxy-4-[(N,N-dimethylamino) methyl] phenyl]-L-phenylalanine ethyl ester / hydrochloride
ESMS: m/z 560 (MH+), mp. 146.5°C.

(0296)

Production Example 260

N-(2,6-dichlorobenzoyl)-4-[2,6-dimethoxy-4-(piperidinomethyl) phenyl]-L-phenylalanine ethyl ester / hydrochloride

ESMS: m/z 600 (MH+), mp. 205.5°C.

(0297)

Production Example 261

N-(2,6-dichlorobenzoyl)-4-[2,6-dimethoxy-4-(morpholinomethyl) phenyl]-L-phenylalanine ethyl ester / hydrochloride

ESMS: m/z 601 (MH+), mp. 177.5°C.

(0298)

Production Example 262

N-(2,6-dichlorobenzoyl)-4-[2,6-dimethoxy-4-[(1-piperazinyl) methyl] phenyl]-L-phenylalanine.

1) N-(2,6-dichlorobenzoyl)-4-[2,6-dimethoxy-4-[(4-t-butoxycarbonyl-1-piperazinyl) methyl] phenyl]-L-phenylalanine ethyl ester was obtained by the same process as in description of Production Example 253 except that 2,6-dimethoxy-4-(thiomorpholinomethyl) benzene boronic acid was replaced by 2,6-dimethoxy-4-[(4-t-butoxycarbonyl-1-piperazinyl) methyl] benzene boronic acid.

2) Methylene chloride / TFA (5 mL /3 mL) solution of the product obtained as above (0.09 g) was stirred at room temperature for three hours. The mixture was evaporated, and the residue was distributed with ethyl acetate and saturated sodium bicarbonate. The ethyl acetate layer was washed with water, dried, and evaporation was caused, and N-(2,6-dichlorobenzoyl)-4-[2,6-dimethoxy-4-[(1-piperazinyl) methyl] phenyl]-L-phenylalanine ethyl ester (70 mg) was obtained.

ESMS: m/z 600 (MH+).

3) The product obtained as above was hydrolysed by process same as in description of Production Example 1-5), and the title compound (50 mg) was obtained.

ESMS: m/z 572 (MH+).

(0299)

Production Example 263

N-(2,6-dichlorobenzoyl)-4-[2,6-dimethoxy-4-(thiomorpholinomethyl) phenyl]-L-phenylalanine S-oxide (263B) and N-(2,6-dichlorobenzoyl)-4-[2,6-dimethoxy-4-(thiomorpholinomethyl)

phenyl]-L-phenylalanine S,S-dioxide (263B)

1) The mCPBA (40 mg) was added at -10°C under nitrogen to methylene chloride (3 ml) solution of N-(2,6-dichlorobenzoyl)-4-[2,6-dimethoxy-4-(thiomorpholinomethyl) phenyl]-L-phenylalanine ethyl ester (0.1 g), and the mixture was stirred for two hours. The mixture was diluted with methylene chloride, washed with saturated sodium bicarbonate and aqueous sodium chloride, dried, evaporation was caused, and preparative TLC purification was carried out, and N-(2,6-dichlorobenzoyl)-4-[2,6-dimethoxy-4-(thiomorpholinomethyl) phenyl]-L-phenylalanine ethyl ester S-oxide (49 mg, ESMS: m/z 633 (MH+)) and N-(2,6-dichlorobenzoyl)-4-[2,6-dimethoxy-4-(thiomorpholinomethyl) phenyl]-L-phenylalanine ethyl ester S,S-dioxide (10 mg, ESMS: m/z 649 (MH+)) were obtained.

2) Two products obtained as above were separately hydrolysed by process same as in description of Production Example 1-5), and N-(2,6-dichlorobenzoyl)-4-[2,6-dimethoxy-4-(thiomorpholinomethyl) phenyl]-L-phenylalanine S-oxide (17 mg, mp. 162.8°C, ESMS: m/z 605 (MH+)) and N-(2,6-dichlorobenzoyl)-4-[2,6-dimethoxy-4-(thiomorpholinomethyl) phenyl]-L-phenylalanine S,S-dioxide (7 mg, mp. 230 °C (degradation), ESMS: m/z 649 (MH+)) were obtained.

(0300)

Production Example 264

N-(2,6-dichlorobenzoyl)-4-[2,6-dimethoxy-4-[2-(4-methyl-1-piperazinyl) ethyl] phenyl]-L-phenylalanine.

1) 2,6-dimethoxy-4-(2-hydroxyethyl) benzene boronic acid was subjected to a coupling reaction according to a production method of description in Production Example 8-3) with N-(2,6-dichlorobenzoyl)-4-bromo-L-phenylalanine ethyl ester, and N-(2,6-dichlorobenzoyl)-4-[2,6-dimethoxy-4-(2-hydroxyethyl) phenyl]-L-phenylalanine ethyl ester (1.3 g) was obtained.
ESMS: m/z 546 (MH+).

2) The product obtained as above (1.25 g) was dissolved in methylene chloride, and Ph_3P (907 mg) was added, and thereafter the solution was cooled to 0°C. CBr_4 (1.14 g) was added to said mixture, and the mixture was stirred at 0°C for two hours. The mixture was distributed with water / ethyl acetate (20 mL each). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (3x20 mL). The organic layers were combined, dried with magnesium sulfate, and evaporation was caused. Silica gel column chromatography (eluate, ethyl acetate / hexane (3 : 7)) purification was carried out on the residue, and N-(2,6-dichlorobenzoyl)-4-[2,6-dimethoxy-4-(2-bromoethyl) phenyl]-L-phenylalanine ethyl ester (1.1 g) was obtained.

ESMS: m/z 610 (MH+).

3) The product obtained as above (200 mg) was dissolved in methylene chloride (3 ml), and N-methylpiperazine (0.11 ml) was added. The mixture was stirred at room temperature for 40 hours, and evaporation was caused. Silica gel column chromatography (eluate, methylene chloride / ethanol (96 : 4)) purification was carried out on the residue, and N-(2,6-dichlorobenzoyl)-4-[2,6-dimethoxy-4-[2-(4-methyl-1-piperazinyl) ethyl] phenyl]-L-phenylalanine ethyl ester (113 mg) was obtained.
ESMS: m/z 628 (MH+).

4) The product obtained as above was hydrolysed using LiOH as described in Production Example 1-5), and N-(2,6-dichlorobenzoyl)-4-[2,6-dimethoxy-4-[2-(4-methyl-1-piperazinyl) ethyl) phenyl]-L-phenylalanine was obtained.
mp. 178.9°C. ESMS: m/z 600 (MH+).

(0301)

Production Example 265

N-(2,6-dichlorobenzoyl)-4-[2,6-dimethoxy-4-(2-piperidino ethyl) phenyl]-L-phenylalanine

The title compound was synthesized using the same procedures as in description of Production Example 264 except that N-methylpiperazine was replaced by piperidine.
mp. 194.9°C. ESMS: m/z 585 (MH+).

(0302)

Production Example 266

N-(2,6-dichloro thiobenzoyl)-4-(2,6-dimethoxyphenyl)-L-phenylalanine.

1) Xylene (10 ml) mixture of N-(2,6-dichlorobenzoyl)-4-(2,6-dimethoxyphenyl)-L-phenylalanine methyl ester (0.25 g) and Lawesson's reagent (2,4-bis [4-methoxyphenyl]-1,3-dithia-2,4-diphosphetane-2,4-disulfide, 0.21 g) was refluxed overnight. The mixture was cooled to about 50°C, and water (15 ml) was added, and it was refluxed for two hours. The mixture was stirred at room temperature overnight, and evaporation was caused. The residue was distributed between ethyl acetate and water. The ethyl acetate layer was washed with water and was dried, and evaporation was caused, and N-(2,6-dichloro thiobenzoyl)-4-(2,6-dimethoxyphenyl)-L-phenylalanine methyl ester (0.25 g) was obtained.
ESMS: m/z 504 (MH+).

2) The product obtained as above was hydrolysed using LiOH as described in Production Example 1-5). Silica gel column chromatography (eluate, methylene chloride / methanol (95 : 5))

purification was carried out with the crude product, and the title compound (25 mg) was obtained.
mp. 180.4°C, ESMS: m/z 490 (MH+).

(0303)

Production Example 267

N-(2,6-dichlorobenzoyl)-4-(2,6-dimethoxyphenyl)-L-phenylalanine N-(methylsulfonyl) amide

1) To N-(2,6-dichlorobenzoyl)-4-(2,6-dimethoxyphenyl)-L-phenylalanine (0.1 g) dissolved in THF (5 ml) were added oxalyl chloride (0.055 ml) and continuingly one drop of DMF at 0°C under nitrogen. The solution was stirred at 0°C for two hours and continuingly at room temperature for two hours. THF was evaporated, and fresh THF (5 ml) was added, and the solution was evaporated once again. This step was repeated further once again, and the residue was dried under vacuum, and N-(2,6-dichlorobenzoyl)-4-(2,6-dimethoxyphenyl)-L-phenylalanyl chloride was obtained.

2) To THF (10 ml) solution of the product obtained as above were added $MeSO_2NH_2$ (0.0292 g) and continuing DBU (0.035 ml). The mixture was stirred at room temperature for four hours and was heated under reflux for two hours. The mixture was evaporated and the residue was purified with silica gel column chromatography (eluate, methylene chloride-3 % methylene chloride / methanol)) and recrystallised from methylene chloride / diethyl ether, and the title compound (25 mg) was obtained.
ESMS: m/z 551 (MH+).

(0304)

Production Example 268

N-(2,6-dichlorobenzoyl)-4-(2,6-dimethoxyphenyl)-L-phenylalanine N-hydroxy amido

Sodium bicarbonate (0.21 g) was added to THF / water (5 mL each) solution of NH_2OH/ hydrochloride (0.14 g) at 0°C, and the mixture was stirred for 30 minutes. N-(2,6-dichlorobenzoyl)-4-(2,6-dimethoxyphenyl)-L-phenylalanyl chloride (0.1 g) dissolved in THF (5 ml) was added to the said mixture at 0°C, and the mixture was stirred overnight at room temperature. The mixture was distributed between ethyl acetate and water. The ethyl acetate layer was washed successively with 1N hydrochloric acid and aqueous sodium chloride, and drying and evaporation were carried out. Silica gel preparative TLC (eluate, 8 % methylene chloride / methanol) purification was carried out on the residue, and the title compound (27 mg) was obtained.
ESMS: m/z 489 (MH+).

(0305)

Production Example 269

N-(2,6-dichlorobenzoyl)-4-(2-methoxyphenyl)-L-phenylalanine N-hydroxy amido

1) To methylene chloride (5 ml) solution of N-(2,6-dichlorobenzoyl)-4-(2-methoxyphenyl)-L-phenylalanine (0.098 g) and t-butylhydroxylamine (0.047 g) were added BOP reagent (0.17 g) and DIEA (0.1 ml) successively, and the mixture was stirred overnight at room temperature. The mixture was evaporated, and the residue was dissolved in ethyl acetate (30 ml). The ethyl acetate solution was washed successively with 1N hydrochloric acid, saturated sodium bicarbonate and saturated LiCl, dried with magnesium sulfate, and it was concentrated. The residue was purified with silica gel preparative TLC (eluate, hexane / ethyl acetate / methylene chloride (6 : 1 : 1)) and recrystallised from methylene chloride / hexane and, and N-(2,6-dichlorobenzoyl)-4-(2-methoxyphenyl)-L-phenylalanine N-(t-butyl)-N-hydroxy amido (74 mg) was obtained.
ESMS: m/z 515 (MH+).

2) Methylene chloride / TFA (3 mL each) solution of the product obtained as above (0.030 g) was stirred at room temperature for 72 hours. The mixture was evaporated, and silica gel column chromatography (eluate, methylene chloride-5 % methylene chloride / methanol) purification was carried out on the residue, and the title compound (10 mg) was obtained.
ESMS: m/z 459 (MH+).

(0306)

Production Example 270

(1S)-N-(2,6-dichlorobenzoyl)-2-[4-(2,6-dimethoxyphenyl) phenyl]-1-(1H-tetrazol-5-yl) ethylamine

The title compound was produced according to a production method in accordance with J. Med. Chem. 41, 1513-1518, 1998.

1) DMF (5 ml) solution of N-(2,6-dichlorobenzoyl)-4-(2,6-dimethoxyphenyl)-L-phenylalanine (0.17 g), HOBT (0.08 g), DIEA (0.19 ml) and 2-cyanoethyl amine (0.03 ml) was stirred at room temperature under nitrogen. EDC (0.14 g) was added after 10 minutes, and the mixture was stirred at room temperature under nitrogen. The mixture was diluted with water, and extraction was carried out with ethyl acetate. The liquid extract was washed successively with water, 1N hydrochloric acid, saturated sodium bicarbonate and aqueous sodium chloride, and was dried, and evaporation was caused, and N-(2,6-dichlorobenzoyl)-4-(2,6-dimethoxyphenyl)-L-phenylalanine N-(2-cyanoethyl) amide (0.17 g) was obtained.
ESMS: m/z 526 (MH+).

2) Ph_3P (0.21g) was added to the product obtained as above (0.17 g) dissolved in acetonitrile (10

ml). The mixture was cooled to 0°C, and DIAD (0.16 ml) and $TMSN_3$ (0.11 ml) were added. The mixture was warmed to room temperature and was heated at 40°C for one hour and was cooled to room temperature, and it was stirred overnight. The mixture was distributed between ethyl acetate and water. The organic layer was washed successively with saturated sodium bicarbonate and aqueous sodium chloride, dried with magnesium sulfate, filtered, and evaporation was caused. Silica gel column chromatography (eluate, ethyl acetate /hexane (1 : 1)) purification was carried out on the residue, and (1S)-N-(2,6-dichlorobenzoyl)-2-[4-(2,6-dimethoxyphenyl) phenyl]-1-[1-(2-cyanoethyl)-1H-tetrazol-5-yl] ethylamine (0.076 mg) was obtained.
ESMS: m/z 551 (MH+).

3) To the product obtained as above (0.073 g) dissolved in chloroform (5 ml) was added DBU (0.059 ml), and the mixture was stirred at room temperature under nitrogen for 48 hours. The mixture was diluted with ethyl acetate, washed with 1N hydrochloric acid and aqueous sodium chloride and dried, and evaporation was caused, and the title compound (0.067 g) was obtained.
ESMS: m/z 498(MH+).

The following compounds (Production Examples 271-274) were produced by a production method same as in description of Production Example 270-1).

(0307)

Production Example 271

N-(2,6-dichlorobenzoyl)-4-(2,6-dimethoxyphenyl)-L-phenylalanine 2-(dimethylamino) ethyl ester.
ESMS: m/z 582 (MH+).

(0308)

Production Example 272

N-(2,6-dichlorobenzoyl)-4-(2,6-dimethoxyphenyl)-L-phenylalanine 2-pyridylmethyl ester
ESMS: m/z 582 (MH+).

(0309)

Production Example 273

N-(2,6-dichlorobenzoyl)-4-(2,6-dimethoxyphenyl)-L-phenylalanine 3-pyridylmethyl ester
ESMS: m/z 582 (MH+).

(0310)

Production Example 274

N-(2,6-dichlorobenzoyl)-4-(2,6-dimethoxyphenyl)-L-phenylalanine 4-pyridylmethyl ester

ESMS: m/z 582 (MH+).

(0311)

Production Example 275

N-(2,6-dichlorobenzoyl)-4-(2,6-dimethoxyphenyl)-L-phenylalanine isopropyl ester

Hydrochloric acid gas was blown to THF / 2-propanol (2/5 mL) solution of N-(2,6-dichlorobenzoyl)-4-(2,6-dimethoxyphenyl)-L-phenylalanine (0.15 g) for 15 minutes, and the solution was stirred overnight at room temperature. The mixture was saturated with hydrochloric acid gas, left to stand at room temperature overnight and evaporated. The residue was distributed between ethyl acetate and water. The ethyl acetate layer was washed with water, and drying and evaporation were carried out, and the residue was purified with column chromatography (eluate, ethyl acetate / hexane (1 : 1)) and triturated with hexane / diethyl ether (5 : 0.5), and the title compound (0.1 g) was obtained.

ESMS: m/z 516 (MH+).

(0312)

Production Example 276

N-(2,6-dichlorobenzoyl)-4-(2,6-dimethoxyphenyl)-L-phenylalanine cyclohexyl ester

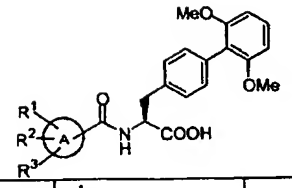
The title compound was produced with similar form in Production Example 275 with replacing 2-propanol by cyclohexanol.

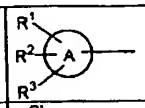
ESMS: m/z 556 (MH+).

The following compounds (Production Examples 277-286) were produced by process same as in description of Production Example 1 or 2 except that 2,6-dichloro benzoic acid or 2,6-benzoyl chloride was replaced by suitable substituted benzoic acid or acid chloride thereof.

(0313)

Table 21



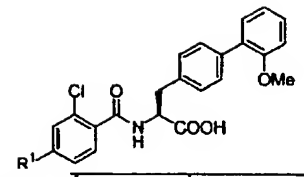
Production Example		m/z MH+
277		455
278		564(M-H)-
279		460
280		448
281		420
282		431
283		438
284		451
285		498
286		498

(0314)

(S)-2-phenylpropionic acid was replaced by suitable substituted 2-chlorobenzoic acid but otherwise the procedures were similar to those described in Production Example 2, and the following compounds (Production Examples 287-290) were produced.

(0315)

Table 22



Production Example	R¹	m/z
287		475 (MH⁺)
288		543 (MH⁺)
289		569 (M-H)⁻
290		501 (M-H)⁻

【0316】製造例291：N-[2-クロロ-4-(2

(0316)

Production Example 291

N-[2-chloro-4-(2-hydroxymethyl-1-pyrrolyl) benzoyl]-4-(2-methoxyphenyl)-L-phenylalanine

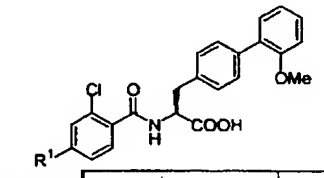
The title compound was obtained from N-[2-chloro-4-(2-formyl-1-pyrrolyl) benzoyl]-4-(2-methoxyphenyl)-L-phenylalanine methyl ester by the reduction using NaBH4 and continuing by saponification using LiOH in accordance with Production Example 50.

ESMS: m/z 503 (M-H)-.

The following compounds (Production Examples 292-293) were produced by process same as in description of Production Example 2.

(0317)

Table 23



Production Example	R¹	m/z
292		510
293		493

【0318】製造例294：N-(2,6-ジクロロベン

(0318)

Production Example 294

N-(2,6-dichlorobenzoyl)-3-[5-(2,6-dimethoxyphenyl)-2-thienyl]-L-alanine

1) N-(9-fluorenylmethoxycarbonyl)-3-(5-bromo-2-thienyl)-L-alanine (813 mg) was dissolved in

ethanol (15 ml), and hydrochloric acid (gas) was blown to said solution at 0°C for five minutes. The mixture was warmed to 50°C and was stirred for one hour. It was cooled to room temperature, and next the solvent was evaporated. Silica gel column chromatography (eluate, hexane-hexane / ethyl acetate (1 : 1)) purification was carried out on the residue, and N-(9-fluorenylmethoxycarbonyl)-3-(5-bromo-2-thienyl)-L-alanine ethyl ester (767 mg) was obtained.
ESMS: m/z 500(MH+).

2) Piperidine (1 ml) was added to methylene chloride (10 ml) solution of product obtained as above (758 mg). The mixture was warmed to 45°C, and evaporated with stirring for two hours. The residue was dissolved in methylene chloride (10 ml) and Et_3N (1.1 ml). To this solution, 2,6-dichlorobenzoyl chloride (240 μL) was added, and the mixture was stirred overnight at room temperature. 1N hydrochloric acid (20 ml) was added, and the mixture was extracted with ethyl acetate. The liquid extract was dried (Na_2SO_4), filtered and evaporated. Silica gel column chromatography (eluate, hexane-hexane / ethyl acetate (1 : 1)) purification was carried out on the residue, and N-(2,6-dichlorobenzoyl)-3-(5-bromo-2-thienyl)-L-alanine ethyl ester (650 mg) was obtained.
ESMS: m/z 450 (MH+).

3) The title compound was produced from the product obtained as above according to a production method of description in Production Example 7-2) and 3).
ESMS: m/z 480 (MH+), mp. 134°C (degradation).

(0319)

Production Example 295

N-(2,6-dichlorobenzoyl)-4-(2,6-dimethoxyphenyl)-L-homo phenylalanine

The title compound was produced using the same procedures as in description of Production Example 5.
ESMS: m/z 488 (MH+), mp. 105-107°C.

(0320)

Production Example 296

N-(2,6-dichlorobenzoyl)-3-ethyl-4-(2-methoxyphenyl)-L-phenylalanine

To N-(2,6-dichlorobenzoyl)-3-(1-hydroxyethyl)-4-(2-methoxyphenyl)-L-phenylalanine ethyl ester (0.08 g) dissolved in acetonitrile (3 ml) were added at 0°C Et_3SiH (0.075 ml) and subsequently and BF_3 etherate (0.0197 ml). The mixture was warmed to room temperature and was stirred for one hour. The reaction was terminated using CH_3OH / water, and the mixture was extracted with methylene chloride. The organic layer was dried with magnesium sulfate, filtered and evaporated. Silica gel preparative TLC (eluate, ethyl acetate / hexane (1 : 2)) purification was

carried out on the residue, and N-(2,6-dichlorobenzoyl)-3-ethyl-4-(2-methoxyphenyl)-L-phenylalanine ethyl ester (39 mg) was obtained.
ESMS: m/z 500 (MH+).

2) The product obtained as above was hydrolysed using LiOH as described in Production Example 1-5) and the title compound (30 mg) was obtained.
mp. 105-107°C, ESMS: m/z 472 (MH+).

(0321)

Production Example 297

N-(2,6-dichlorobenzoyl)-4-(2,6-dimethoxyphenyl)-3-acetylamino-L-phenylalanine

1) N-(2,6-dichlorobenzoyl)-4-(2,6-dimethoxyphenyl)-3-nitro-L-phenylalanine ethyl ester was produced by replacing N-(t-butoxycarbonyl)-L-tyrosine ethyl ester with N-t-butoxycarbonyl-3-nitro-L-tyrosine ethyl ester using the same procedures as in the description of Production Example 1.

2) The product obtained as above (1.07 g) was dissolved in methanol (15 ml) under nitrogen. Raney nickel (100 mg) was added, and H_2 gas was blown in the said mixture for 15 minutes. Stirring was continued for six hours under H_2. The mixture was filtered with celite and washed with methanol, and the filtrate was evaporated. Silica gel column chromatography (eluate, hexane-hexane / ethyl acetate (1 : 1)) purification was carried out on the residue, and N-(2,6-dichlorobenzoyl)-4-(2,6-dimethoxyphenyl)-3-amino-L-phenylalanine ethyl ester (845 mg) was obtained.
ESMS: m/z 503 (MH+).

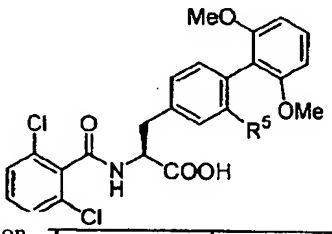
3) The product obtained as above (119 mg) was dissolved in methylene chloride (1 ml) and pyridine (57 μl). To this solution, acetic anhydride (45 μL) was added, and the mixture was stirred at room temperature for 18 hours. The mixture was evaporated, and silica gel column chromatography (eluate, hexane-ethyl acetate) purification was carried out on the residue, and N-(2,6-dichlorobenzoyl)-4-(2,6-dimethoxyphenyl)-3-acetylamino-L-phenylalanine ethyl ester (127 mg) was obtained.
ESMS: m/z 545 (MH+).

4) The product obtained as above (126 mg) was hydrolysed using LiOH as described in Production Example 1-5) and the title compound (98 mg) was obtained.
mp. 142-144°C. ESMS: m/z 531 (MH+).

The following compounds (Production Examples 298-299) were produced by a production method same as in description of Production Example 297.

(0322)

Table 24



Production Example	R^5	m/z MH^+	mp.°C
298	CH_3SO_2NH	567	118-120
299	EtOCONH	561	216-217

(0323)

Production Example 300

N-(2,6-dichlorobenzoyl)-3-(2-oxo-1-pyrrolidinyl)-4-(2,6-dimethoxyphenyl)-L-phenylalanine

1) To N-(2,6-dimethoxybenzoyl)-3-nitro-4-(2,6-dimethoxyphenyl)-L-phenylalanine methyl ester (1.07 g) dissolved in methanol (15 ml) was added Raney nickel (100 mg), and H_2 gas was blown in the said mixture for 15 minutes. The mixture was filtered with celite, and the filtrate was evaporated under reduced pressure. Silica gel column chromatography (eluate, hexane-hexane / ethyl acetate (1 : 1)) purification was carried out on the residue, and N-(2,6-dichlorobenzoyl)-3-amino-4-(2,6-dimethoxyphenyl)-L-phenylalanine methyl ester (845 mg) was obtained.
ESMS: m/z 503 (MH+).

2) 4-chloro butyryl chloride (54 μl) was added to methylene chloride (1 ml) of product obtained as above (122 mg) and pyridine (78 μl) solution. The mixture was stirred at room temperature for 12 hours, and concentration was carried out under reduced pressure. Silica gel column chromatography (eluate, hexane-ethyl acetate) purification was carried out on the residue, and N-(2,6-dichlorobenzoyl)-3-(4-chloro butyryl amino)-4-(2,6-dimethoxyphenyl)-L-phenylalanine methyl ester (56 mg) was obtained.
ESMS: m/z 607 (MH+).

3) To product obtained as above (56 mg) dissolved in DMF (1 ml) was added NaH (11 mg, in 60 % oil), and the mixture was stirred at room temperature for 30 minutes. 1N hydrochloric acid was added to the said mixture, and the mixture was extracted with ethyl acetate. The liquid extract was dried (Na_2SO_4) and evaporated. Silica gel column chromatography (eluate, methylene

chloride-10 % methanol / methylene chloride) purification was carried out on the residue, and the title compound (23 mg) was obtained.
ESMS: m/z 557 (MH+).

(0324)

The following compounds (Production Examples 301-302) were produced by replacing 2-phenylpropionic acid with necessary benzoic acid, and 4-(2-methoxyphenyl)-L-phenylalanine methyl ester / hydrochloride with 4-(2,6-dimethoxyphenyl)-L-phenylalanine methyl ester / hydrochloride in a similar form in accordance with Production Example 2.

(0325)

Production Example 301

N-(2,6-dichloro-4-phenylbenzoyl)-4-(2,6-dimethoxyphenyl)-L-phenylalanine
ESMS: m/z 550 (MH+), mp. 215°C.

(0326)

Production Example 302

N-[2,6-dichloro-4-(1-methyl-2-pyrrolyl) benzoyl]-4-(2,6-dimethoxyphenyl)-L-phenylalanine
ESMS: m/z 553 (MH+), mp. 199°C.

(0327)

Production Example 303

N-[4-(2-pyrrolyl)-2, 6-dichlorobenzoyl]-4-(2,6-dimethoxyphenyl)-L-phenylalanine

1) N-(4-bromo-2,6-dichlorobenzoyl)-4-(2,6-dimethoxyphenyl)-L-phenylalanine methyl ester (0.410 g) was subjected to a coupling reaction with 1-t-butoxycarbonyl-2-pyrrole boronic acid (0.930 g) / THF (10 ml) in accordance with Production Example 7-2), and N-[4-(1-t-butoxycarbonyl-2-pyrrolyl)-2,6-dichlorobenzoyl]-4-(2,6-dimethoxyphenyl)-L-phenylalanine methyl ester (0.435 g) was obtained.
ESMS: m/z 653 (MH+).

2) The compound obtained as above was treated with TFA as described in Production Example 1-3), and N-[4-(2-pyrrolyl)-2,6-dichlorobenzoyl]-4-(2,6-dimethoxyphenyl)-L-phenylalanine methyl ester (0.198 g) was obtained.
ESMS: m/z 553 (MH+).

3) The product obtained as above (0.170 g) was hydrolysed using LiOH as described in Production Example 1-5), and the title compound (0.127 g) was obtained.

ESMS: m/z 539 (MH+), mp. 250°C.

(0328)

Production Example 304

N-[4-(5-pyrazolyl)-2,6-dichlorobenzoyl)-4-(2,6-dimethoxyphenyl)-L-phenylalanine

1) N-(4-bromo-2,6-dichlorobenzoyl)-4-(2,6-dimethoxyphenyl)-L-phenylalanine methyl ester (0.240 g) was subjected to a coupling reaction with 1-[[2-(trimethylsilyl) ethoxy] methyl]-5-pyrazole boronic acid (0.343 g) dissolved in THF (10 ml) in accordance with Production Example 7-2), and N-[4-[1-[[2-(trimethylsilyl) ethoxy] methyl]-5-pyrazolyl]-2,6-dichlorobenzoyl]-4-(2,6-dimethoxyphenyl)-L-phenylalanine methyl ester (0.277 g) was obtained.
ESMS: m/z 684 (MH+) and 682 (M-H)-.

2) To product obtained as above (0.277 g) dissolved in methanol (10 ml) was added concentrated hydrochloric acid (0.20 ml), and after 3 hours, the second addition of concentrated hydrochloric acid (0.20 ml) was carried out. The mixture was stirred at room temperature overnight, and thereafter, it was concentrated. The residue was dissolved in ethyl acetate, washed with sodium bicarbonate and aqueous sodium chloride, dried with sodium sulfate, filtered and concentrated. Silica gel preparative TLC (eluate, hexane-hexane / ethyl acetate (1 : 1)) purification was carried out on the residue, and N-[4-(5-pyrazolyl)-2,6-dichlorobenzoyl]-4-(2,6-dimethoxyphenyl)-L-phenylalanine methyl ester (0.148 g) was obtained.
ESMS: m/z 554 (MH+).

3) The product obtained as above was hydrolysed as described in Production Example 1-5) and the title compound (0.133 g) was obtained.
ESMS: m/z 540 (MH+) and 652 (M-+ TFA), mp. 156°C.

(0329)

Production Example 305

N-[3-(3,5-dimethyl-4-isoxazolyl)-2,6-dichlorobenzoyl]-4-(2,6-dimethoxyphenyl)-L-phenylalanine

The title compound was produced starting from the N-(3-bromo-2,6-dichlorobenzoyl)-4-(2,6-dimethoxyphenyl)-L-phenylalanine methyl ester using the same procedures as in the description of Production Example 303.
MS: m/z 569 (MH+), mp. 144.8°C.

(0330)

Production Example 306

N-[4-(1,3-thiazol-2-yl)-2,6-dichlorobenzoyl]-4-(2,6-dimethoxyphenyl)-L-phenylalanine

1) To N-(4-bromo-2,6-dichlorobenzoyl)-4-(2,6-dimethoxyphenyl)-L-phenylalanine methyl ester (0.240 g) dissolved in toluene (10 ml) were added 2-tributyl stannio-1,3-thiazole (0.52 g) and $Pd(PPh_3)_4$ (0.11 g), and the solution was heated to 80°C under nitrogen for 24 hours. It was worked up, and was refined using the same procedures as in description of Production Example 135-3), and N-[4-(1,3-thiazol-2-yl)-2,6-dichlorobenzoyl]-4-(2,6-dimethoxyphenyl)-L-phenylalanine methyl ester (30 mg) was obtained.
ESMS: m/z 571 (MH+).

2) The product obtained as above was hydrolysed by process same as in description of Production Example 1-5), and the title compound (22.7 mg) was obtained.
ESMS: m/z 557 (MH+), mp. 141.9°C.

(0331)

Production Example 307

N-[4-(1,3-thiazol-4-yl)-2,6-dichlorobenzoyl]-4-(2,6-dimethoxyphenyl)-L-phenylalanine

The title compound was produced by replacing 2-tributyl stannio-1,3-thiazole with 4-tributyl stannio-1,3-thiazole using similar procedures as in Production Example 306.
ESMS: m/z 557 (MH+) and 555 (M--H), mp. 186.5°C.

(0332)

Production Example 308

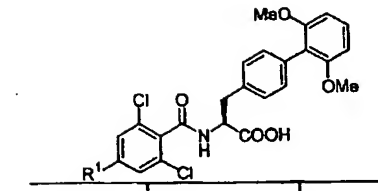
N-[4-(2-pyrazinyl)-2,6-dichlorobenzoyl]-4-(2,6-dimethoxyphenyl)-L-phenylalanine

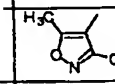
2-tributyl stannio-1,3-thiazole was replaced by 2-tributyl stannio pyrazine but otherwise the procedures were similar to those described in Production Example 306, and the title compound was produced.
ESMS: m/z 552 (MH+), mp. 145.7°C.

The following compounds (Production Examples 309-318) were produced by process same as in description of Production Example 303.

(0333)

Table 25



Production Example	R¹	m/z (MH⁺)
309		569
310		558
311		551
312		551
313		552
314		553
315		557
316		556
317		557
318		550

(0334)

Production Example 319

N-(2,6-dichlorobenzoyl)-4-[2,6-dimethoxy-3-(morpholinomethyl) phenyl]-L-phenylalanine

1) 2,6-dimethoxy-3-(hydroxymethyl) benzene boronic acid was subjected to a coupling reaction with N-(2,6-dichlorobenzoyl)-4-bromo-L-phenylalanine ethyl ester by a process same as in description of Production Example 7-2), and N-(2,6-dichlorobenzoyl)-4-[2,6-dimethoxy-3-(hydroxymethyl) phenyl]-L-phenylalanine ethyl ester was obtained.

2) Thionyl chloride (100 ml) was added under nitrogen to ice cooled solution of methylene chloride (5 ml) of product obtained as above (0.212 mg). The mixture was stirred at room temperature for one hour, and evaporation was caused. The residue was dissolved in methylene chloride, evaporated and dried under vacuum, and N-(2,6-dichlorobenzoyl)-4-[2,6-dimethoxy-3-(chloromethyl) phenyl]-L-phenylalanine ethyl ester (0.22 g) of crude product was obtained.

3) The product obtained as above (0.22 g) dissolved in DMF (5 ml) solution was added under

nitrogen to ice cooled solution of DMF (1 ml) containing Et_3N (0.111 ml) of morpholine (41 mg). The mixture was stirred at room temperature for 14 hours, and thereafter, it was distributed between ethyl acetate and water. The ethyl acetate layer was separated, washed successively with saturated sodium bicarbonate, water and aqueous sodium chloride, and drying and evaporating were carried out. Silica gel column chromatography (eluate, ethyl acetate) purification was carried out on the residue, and N-(2,6-dichlorobenzoyl)-4-[2,6-dimethoxy-3-(morpholinomethyl) phenyl]-L-phenylalanine ethyl ester (0.186 g) was obtained.
ESMS: m/z 601 (MH+).

4) The product obtained as above was hydrolysed by process same as in description of Production Example 1-5), and the title compound was obtained.
ESMS: m/z 573 (MH+), mp. 241-242°C.

(0335)

Production Example 320

N-(2,6-dichloro-4-fluorobenzoyl)-4-(2,6-dimethoxyphenyl)-L-phenylalanine

The title compound was produced by process same as in description of Production Example 2.
MS: m/z 492 (MH+), mp. 206-207°C.

(0336)

Production Example 321

N-(2,6-dichlorobenzoyl)-4-[2,6-dimethoxy-4-(trifluoromethyl) phenyl]-L-phenylalanine

The title compound was produced by process same as in description of Production Example 2.
MS: m/z 542 (MH+), mp. 231-232°C.

(0337)

Production Example 322

N-(2,6-dichlorobenzoyl)-4-(2,6-dimethoxy-3-bromo phenyl)-L-phenylalanine

1) N-(2,6-dichlorobenzoyl)-4-(2,6-dimethoxyphenyl)-L-phenylalanine methyl ester (1.01 g) was dissolved in methylene chloride (40 ml) under nitrogen, and tetrabutyl ammonium bromide (1.21 g) was added, and the mixture was stirred overnight at room temperature. Tetrabutyl ammonium bromide (0.55 g) was further added, and the mixture was stirred for one day. Thereafter, mixture was washed with water (25 ml), and the organic layer was dried with magnesium sulphate, filtered and evaporated. Silica gel flash column chromatography (eluate, hexane and ethyl acetate) purification was carried out on the residue, and N-(2,6-dichlorobenzoyl)-4-(2,6-dimethoxy-3-bromo phenyl)-L-phenylalanine methyl ester (1.17 g) was obtained.

2) The product obtained as above was hydrolysed using the same procedures as in description of Production Example 1-5), and the title compound was obtained.

MS: m/z 555 (MH+), mp. 205-206°C.

(0338)

Production Example 323

N-(2,6-dichlorobenzoyl)-4-(2,6-dimethoxy-3-aminophenyl)-L-phenylalanine

1) N-(2,6-dichlorobenzoyl)-4-(2,6-dimethoxyphenyl)-L-phenylalanine methyl ester (1.59 g) was dissolved in THF (4 ml) under nitrogen, and thereafter, 70 % HNO_3 (4 ml) was added, and the mixture was stirred overnight at 50°C. The mixture was diluted with ethyl acetate (150 ml) and washed with water (100 ml). The organic layer was dried with magnesium sulfate, filtered and evaporated. The residue was dissolved in anhydrous methanol (100 ml) and dried hydrochloric acid gas was blown in the said mixture at 0°C for several minutes. The mixture was stirred at room temperature overnight, concentrated, dissolved in ethyl acetate and washed with 1N hydrochloric acid, saturated sodium bicarbonate and aqueous sodium chloride. The organic layer was dried with magnesium sulfate, filtered, and evaporation was caused. Silica gel flash column chromatography (eluate, hexane and ethyl acetate) purification was carried out with the crude product, and N-(2,6-dichlorobenzoyl)-4-(2,6-dimethoxy-3-nitrophenyl)-L-phenylalanine methyl ester (1.1 g) was obtained.

2) The product obtained as above was dissolved in ethanol (40 ml), and $Na_2S_2O_4$ (2.6 g) / water (5 ml) was added. The mixture was refluxed for two hours, and it was concentrated. The residue was dissolved using ethyl acetate and was washed with aqueous sodium chloride. The organic layer was dried with magnesium sulfate, filtered and evaporated. Silica gel preparative TLC (eluate, hexane and ethyl acetate) purification was carried out on the residue, and N-(2,6-dichlorobenzoyl)-4-(2,6-dimethoxy-3-aminophenyl)-L-phenylalanine methyl ester (0.31 g) was obtained.

3) The product obtained as above was hydrolysed by process same as in description of Production Example 1-5), and the title compound was obtained.

MS: m/z 542 (MH+), mp. 231-232°C.

(0339)

Production Example 324

N-(2,6-dichlorobenzoyl)-4-[2,6-dimethoxy-3-(methyl ureide) phenyl]-L-phenylalanine

N-(2,6-dichlorobenzoyl)-4-(2,6-dimethoxy-3-aminophenyl)-L-phenylalanine methyl ester was reacted with MeNCO instead of MeNCS by a production method same as in description of

Production Example 70, and the title compound was obtained.

MS: m/z 546(MH+), mp. 236-237°C.

(0340)

Production Example 325

N-(2,6-dichlorobenzoyl)-4-[2,6-dimethoxy-3-(acetylamino) phenyl]-L-phenylalanine

N-(2,6-dichlorobenzoyl)-4-(2,6-dimethoxy-3-aminophenyl)-L-phenylalanine methyl ester and acetyl chloride were reacted by a production method same as in description of Production Example 67, and the title compound was thereby obtained.

MS: m/z 531 (MH+), mp. 244-245°C.

(0341)

Production Example 326

N-(2,6-dichlorobenzoyl)-4-(2,6-dimethoxy-3-carbamoyl phenyl)-L-phenylalanine

1) N-(2,6-dichlorobenzoyl)-4-(2,6-dimethoxyphenyl)-L-phenylalanine methyl ester (150 mg) was dissolved in acetonitrile (6 ml) under nitrogen, and chloro sulfonyl isocyanate (45 μl) was added, and the mixture was stirred at room temperature for two hours 30 minutes. The mixture was concentrated, and 1N hydrochloric acid (8 ml) was added. The mixture was stirred at room temperature overnight, extracted with ethyl acetate, dried with magnesium sulfate, filtered and evaporated. Silica gel preparative TLC (eluate, ethyl acetate) purification was carried out with the crude product, and N-(2,6-dichlorobenzoyl)-4-(2,6-dimethoxy-3-carbamoyl phenyl)-L-phenylalanine methyl ester (156 mg) was obtained.

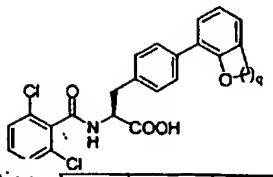
2) The product obtained as above was hydrolysed by process same as in description of Production Example 1-5), and the title compound was obtained.

MS: m/z 517 (MH+), mp. 227-228°C.

By the production method same as in Production Example 7, the following compounds (Production Examples 327-328) were produced respectively from 7-bromo-2,3-dihydrobenzo (b) furan and 8-bromo-3,4-dihydro-2H-benzopyran (Tet. Lett., 1998, 39, 2219-2222 by Kerrigan F., Martin C., Thomas G.H.).

(0342)

Table 26



Production Example	q	ms MH+	融点℃
327	2	466	215-216
328	3	470	214-215

(0343)

Production Example 329

N-(2,6-dichlorobenzoyl)-4-(1-t-butoxycarbonyl-2-pyrrolyl)-L-phenylalanine

The title compound was produced using 1-(t-butoxycarbonyl) pyrrole-2-boronic acid (Frontier Scientific) by process same as in description of Production Example 7.

MS: m/z 503 (MH+), mp. 98-99°C.

(0344)

Production Example 330

N-(2,6-dichlorobenzoyl)-4-(3,5-dimethyl-4-isoxazolyl)-L-phenylalanine

The title compound and methyl ester body thereof were produced by process same as in description of Production Example 7.

MS: m/z 433 (MH+), mp. 119°C.

Methyl ester body of The title compound: MS: m/z 447 (MH+), mp. 152°C.

(0345)

Production Example 331

N-(2,6-dichloro-3-bromobenzoyl)-4-(2,6-dimethoxyphenyl)-L-phenylalanine

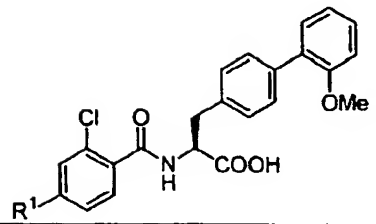
The title compound was produced by process same as in description of Production Example 322.

MS: m/z 553 (MH-), mp. 234.8°C.

The following compounds (Production Examples 332-335) were produced by process same as in description of Production Example 2.

(0346)

Table 27



Production Example	R^1	MS, m/z	mp.°C
332	CH_3NH-	439 (MH^+)	82.8
333	$CH_3SO_2N(CH_3)$-	517 (MH^+)	79.3
334	$(CH_3)_2SO_2NH$-	532 (MH^+)	128.1

(0347)

Production Example 335

N-[2-chloro-4-(methanesulphonyl amino) benzoyl]-4-[2-(trifluoromethyl) phenyl]-L-phenylalanine

The title compound was produced using the same procedures as in description of Production Example 3.

MS: m/z 541 (MH+), mp. 114°C.

(0348)

Production Example 336

N-(2,6-dichlorobenzoyl)-3-chloro-4-(2-methoxyphenyl)-L-phenylalanine

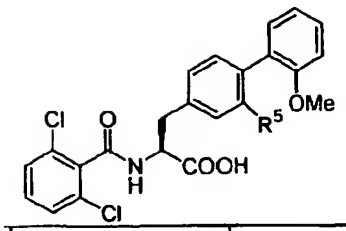
The title compound was produced using N-(t-butoxycarbonyl)-3-chloro-L-tyrosine methyl ester by process same as in description of Production Example 1.

ESMS: m/z 479 (MH+), mp. 131°C.

The following compounds (Production Examples 337-339) were produced by a process same as in description of Production Example 71.

(0349)

Table 28



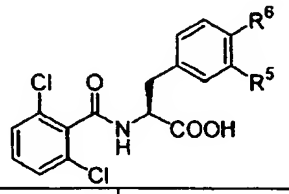
Production Example	R^5	MS m/z (MH+)	mp.°C
337	$-COCH_2CH_3$	500	118-119
338	$-CO(CH_2)_3CH_3$	528	117.6
339	$-CO(CH_2)_5CH_3$	556	86-88

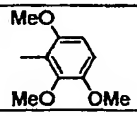
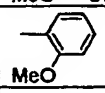
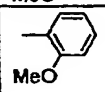
(0350)

The following compounds (Production Examples 340-342) were produced by a production method same as in description of Production Example 73.

(0351)

Table 29



Production Example	R^5	R^6	MS m/z (MH+)	mp.°C
340	$-CH(OH)CH_3$		548	121-123
341	$-CH(OH)CH_2CH_3$		502	117-119
342	$-CH(OH)(CH_2)_3CH_3$		528 (M-H)-	158-159

(0352)

Production Example 343

N-(2,6-dichlorobenzoyl)-3-acetylamino-4-phenyl-L-phenylalanine

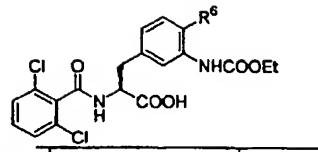
The title compound was produced by a production method same as in description of Production Example 80.

ESMS: m/z 471 (MH+).

The following compounds (Production Examples 344-345) were produced using chloro formic acid ethyl ester by a production method same as in description of Production Example 64.

(0353)

Table 30



Production Example	R^6	MS m/z (MH+)
344		501
345		531

(0354)

Production Example 346

N-(2,6-dichlorobenzoyl)-4-(2,6-dimethoxy-4-hydroxyethyl)-L-phenylalanine

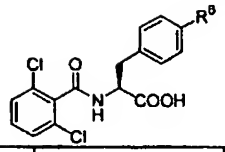
1) DME / water (20 mL /0.5 mL) mixture of 2,6-dimethoxy-4-(t-butyl diphenyl silyloxy) benzene boronic acid (3 g), N-(2,6-dichlorobenzoyl)-4-bromo-L-phenylalanine ethyl ester (0.8 g), $Pd(PPh_3)_4$ (1 g) and potassium carbonate (2.1 g) was heated at 80°C under nitrogen for six hours. The mixture was diluted with ethyl acetate, washed with water, dried and evaporated. The residue was dissolved in ethyl acetate, and the solution was filtered with silica gel column, and evaporation was caused. The residue was dissolved in THF, and TBAF (1.6M THF solution, 4 mL) was added. The mixture was stirred at room temperature for one hour, diluted with water and extraction was carried out with ethyl acetate. The liquid extract was washed with water, and drying and evaporating were carried out. Silica gel flash column chromatography (eluate, ethyl acetate / hexane (1 : 2)) purification was carried out on the residue, and N-(2,6-dichlorobenzoyl)-4-(2,6-dimethoxy-4-hydroxyphenyl)-L-phenylalanine ethyl ester (0.5 g) was obtained.
ESMS: m/z 490 (MH+).

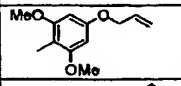
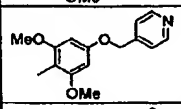
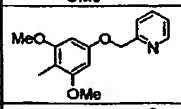
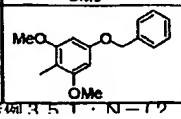
2) The product obtained as above (0.05 g) was hydrolysed using LiOH by process same as in description of Production Example 1-5), and the title compound (0.4 g) was obtained.
ESMS: m/z 490 (MH+).

The following compounds (Production Examples 347-350) were produced by a production method same as in description of Production Example 32.

(0355)

Table 31



Production Example	R^8	MS m/z (MH+)
347		530
348		681
349		581
350		680

(0356)

Production Example 351

N-(2,6-dichlorobenzoyl)-3-[1-(hydroxyimino) ethyl]-4-(2-methoxyphenyl)-1-phenylalanine

1) Hydroxyamine hydrochloride (23 mg) and sodium acetate (40 mg) were added to N-(2,6-dichlorobenzoyl)-3-acetyl-4-(2-methoxyphenyl)-L-phenylalanine ethyl ester (0.15g) dissolved in n-butanol (5 ml). The mixture was refluxed for six hours, and evaporation was caused. The obtained residue was diluted with methylene chloride, washed with 1N hydrochloric acid, and drying and evaporating were carried out. The residue was refined by silica gel preparative TLC (eluate, ethyl acetate / hexane (1 : 1)), and N-(2,6-dichlorobenzoyl)-3-[1-(hydroxyimino) ethyl]-4-(2-methoxyphenyl)-L-phenylalanine ethyl ester was obtained.
ESMS: m/z 490 (MH+).

2) The product obtained as above was hydrolysed with LiOH in the same way as in Production Example 1-5), and the title compound was thereby obtained.
ESMS: m/z 501 (MH+).

(0357)

Production Example 352

N-(2,6-dichlorobenzoyl)-3-[1-(methoxyimino) ethyl]-4-(2-methoxyphenyl)-L-phenylalanine

1) Methoxyamine hydrochloride (24 mg) and DIEA (60 mg) were added to N-(2,6-dichlorobenzoyl)-3-acetyl-4-(2-methoxyphenyl)-L-phenylalanine ethyl ester (0.12 g) dissolved in ethanol (5 ml). The mixture was refluxed for two hours, and evaporation was caused. The obtained residue was diluted with ethyl acetate, washed with 1N hydrochloric acid, and drying and

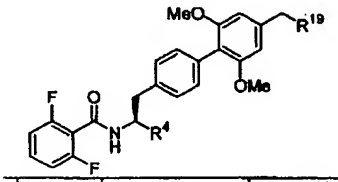
evaporating were carried out. The residue was refined by silica gel preparative TLC (eluate, ethyl acetate / hexane (2 : 1)), and N-(2,6-dichlorobenzoyl)-3-[1-(methoxyimino) ethyl]-4-(2-methoxyphenyl)-L-phenylalanine ethyl ester (0.058 g) was obtained.
ESMS: m/z 534 (M-H)-.

2) The product obtained as above was hydrolysed with LiOH in the same way as in Production Example 1-5), and the title compound (0.04 g) was obtained.
ESMS: m/z 513 (M-H)-, mp.: 106.8°C.

(0358)

The following compounds (Production Examples 353-356) were synthesized in the same way as one example of the aforesaid Production Examples.

Table 32



Production Example	R4	R19	ESMS m/z (MH+)	mp.°C
353	COOH		538	232
354	COOEt	 hydrochlor ide	567	160
355	COOH		553	225
356	COOEt	 dihydrochloride	582	226

(0359)

Production Example 357

N-(2,6-dichlorobenzoyl)-4-[2,6-dimethoxy-4-(succinimide methyl) phenyl]-L-phenylalanine

1) DEAD (0.13 ml) was added to THF (3 ml) ice cooled solution of N-(2,6-dichlorobenzoyl)-4-[2,6-dimethoxy-4-(hydroxymethyl) phenyl]-L-phenylalanine t-butyl ester (250 mg), triphenylphosphine (175 mg) and succinimide (90 mg) under nitrogen. The mixed liquid was stirred at 0°C for 30 minutes, and it was warmed to room temperature and stirred for two hours. The mixed liquid was caused to undergo liquid separation into water and ethyl acetate, and the aqueous layer was extracted with ethyl acetate. The recovered organic layer was dried with magnesium sulfate, and concentrated in vacuum. The residue was refined by TLC for silica gel fractionation (eluate, ethyl acetate /hexane (1 : 1)), and N-(2,6-dichlorobenzoyl)-4-[2,6-dimethoxy-4-(succinimide methyl) phenyl]-L-phenylalanine t-butyl ester (138 mg) was obtained.

2) TFA (2 ml) was added to methylene chloride (4 ml) solution of product obtained as above (120 mg). The mixed liquid was stirred at room temperature for three days, and concentrated in vacuum. The residue was refined by silica gel column chromatography (eluate, methylene chloride / methanol (95 : 5)), recrystallised with ethanol / water, and the title compound (61 mg) was obtained.

mp.: 137°C, ESMS: m/z 608 $(M+Na)^+$.

(0360)

Production Example 358

N-(2,6-dichlorobenzoyl)-4-(2,6-dimethoxy-4-[(3-methyl-2,5-dioxo-1-imidazolidinyl) methyl] phenyl]-L-phenylalanine

The title compound was obtained in the same way as in Production Example 357 except that succinimide was replaced by 1-methyl hydantoin.

mp.: 248°C, ESMS: m/z 624 $(M+Na)^+$.

(0361)

Production Example 359

N-(2,6-dichlorobenzoyl)-4-(6-methoxy-2-hydroxyphenyl)-L-phenylalanine

N-(2,6-dichlorobenzoyl)-4-(6-methoxy-2-hydroxyphenyl)-L-phenylalanine ethyl ester was hydrolysed with LiOH in the same way as in Production Example 1-5), and the title compound was thereby obtained.

mp.: 224.4°C, ESMS: m/z 460 (MH+), 458 (M-H)-.

(0362)

Production Example 360

N-(2,6-dichlorobenzoyl)-4-(2,6-dihydroxyphenyl)-L-phenylalanine

1) 2,6-di (methoxymethoxy) benzene boronic acid (0.25 g) was coupled with N-(2,6-dichlorobenzoyl)-O-(trifluoromethane sulfonyl)-L-tyrosine ethyl ester in the same way as in Production Example 5-3), and N-(2,6-dichlorobenzoyl)-4-[2,6-di (methoxymethoxy) phenyl]-L-phenylalanine ethyl ester was obtained.

ESMS: m/z 562 (MH+).

2) Hydrochloric acid (4N dioxane solution, 1.2 mL) was added to the product obtained as above (0.076 g) dissolved in ethanol (5 ml), and the mixture was stirred at room temperature under nitrogen for four hours. The mixed liquid was evaporated, and N-(2,6-dichlorobenzoyl)-4-(2,6-dihydroxyphenyl)-L-phenylalanine ethyl ester (61.6 mg) was obtained.

ESMS: m/z 474 (MH+).

3) The product obtained as above (61.6 mg) was hydrolysed with LiOH (33.8 mg) in the same way as in Production Example 1-5), and N-(2,6-dichlorobenzoyl)-4-(2,6-dihydroxyphenyl)-L-phenylalanine (58.3 mg) was obtained.
ESMS: m/z 446 (MH+), 444 (M-H)-, mp. 238°C.

(0363)

Reference Examples.

Reference Example 1

2,6-dichlorobenzene boronic acid

1-bromo-2,6-dichlorobenzene (2.00 g) was dissolved in distilled THF (7 ml). This solution was cooled to -78°C, and 1.6M hexane solution (8.3 ml) of n-BuLi was added dropwise to cooled solution under nitrogen. The mixture was stirred at -78°C for five minutes, and (MeO)3B (2.2 ml) was added. The obtained liquid mixture was left to stand until it warmed to room temperature, and was stirred overnight. Water was added, and the obtained mixture was stirred for 0 hours 30 minutes, and thereafter, it was made acidic with acetic acid and extraction was carried out with ethyl acetate. The organic layer was washed furthermore with water and aqueous sodium chloride and was dried with magnesium sulfate, filtered, and distilled off, and 2,6-dichlorobenzene boronic acid (1.6 g) was obtained.

(0364)

Reference Example 2

2,6-dicyanobenzene boronic acid

1,3-dicyanobenzene (1.00 g) was dissolved in distilled THF (70 ml). This solution was cooled to –96 °C and a 2M solution (4.2 ml) of LDA was added dropwise under nitrogen. The mixture was stirred at -96°C for 30 minutes, and (MeO)3B (1.3 ml) was added. The obtained mixture was left to stand until it warmed to room temperature and was stirred overnight. Water was added, and the obtained mixture was stirred for 0 hours 30 minutes, and thereafter, it was made acidic with acetic acid, and extraction was carried out with ethyl acetate. The organic layer was washed with water and aqueous sodium chloride and was dried with magnesium sulfate, filtered, and evaporation was caused. The residue was dissolved in methylene chloride, and it was filtered, and evaporation was caused, and 2,6-dicyanobenzene boronic acid (0.56 g) was obtained.

(0365)

Reference Example 3

2,6-dimethoxy-4-propyl benzene boronic acid

1) ethyl triphenylphosphonium bromide (4.69 g) was dissolved in anhydrous THF (70 ml) and the mixture was cooled to 0-5°C. 2.5M hexane solution (5.05 ml) of n-BuLi was added dropwise, and the obtained mixture was stirred at room temperature for three hours. The mixture was cooled to -78°C and a solution of 3,5-dimethoxybenzaldehyde (2 g) in anhydrous THF (14 ml) was added. The mixture was left to stand until it warmed to room temperature and was stirred overnight. The mixture was concentrated, and the residue was dissolved in ethyl acetate and was washed with water and aqueous sodium chloride and was dried with magnesium sulfate, filtered, and evaporation was caused. The residue was refined by silica gel column chromatography (elution liquid, hexane/ethyl acetate 10:1) and 3,5-dimethoxy-1-(1-propenyl) benzene was obtained as mixture of cis and trans isomer (2.15 g).

2). The product obtained as above was dissolved in ethanol (60 ml), and 10 % Pd/C (215 mg) was added. The mixture was stirred under a hydrogen atmosphere for 19 hours. The mixture was passed through silica pad using methylene chloride as solvent, and it was eliminated by distillation, and 3,5-dimethoxy-1-propyl benzene (1.76 g) was obtained.

3). The product obtained as above was treated in the same way as in Production Example 7-(1), except that 1,3-dimethoxybenzene was replaced by the 3,5-dimethoxy-1-propyl benzene, and the title compound was obtained.

(0366)

Reference Example 4

2,6-dimethoxy-4-trifluoromethyl benzene boronic acid

1) 3-methoxy-5-(trifluoromethyl) aniline (5 g) was suspended in 20 % hydrochloric acid (200 ml) and was stirred for 30 minutes and was cooled to 0-5°C, and NaNO2(2.17g) was added a little at a time, and it was diazotised. The mixture was stirred at the same temperature for 30 minutes, and it was added dropwise to boiling water (200 ml). The mixture was refluxed for 15 minutes and was allowed to cool to room temperature and was extracted with ethyl acetate and was dried with magnesium sulfate, filtered, and evaporation was caused. The residue was refined by silica gel column chromatography (elution liquid, hexane and ethyl acetate) and 3-methoxy-5-(trifluoromethyl) phenol (3.6 g) was obtained.

2. The product obtained as above was dissolved in acetone (20 ml) and potassium carbonate (5.18 g) and iodomethane (1.75 ml) were added. The mixture was stirred at room temperature under nitrogen for two days, and it was eliminated by distillation, and it was dissolved in water (50 ml) and was extracted with methylene chloride, dried with magnesium sulfate, and it was filtered, and it was eliminated by distillation. The residue was refined by silica gel column chromatography (elution liquid, hexane) and desired 3,5-dimethoxy-α, α, α-trifluorotoluene (2.97 g) was obtained.

3. The product obtained as above was treated in the same way as in Production Example 7-(1), except that 1,3-dimethoxybenzene was replaced by the 3,5-dimethoxy-α, α, α-trifluorotoluene, and the title compound was obtained.

(0367)

Reference Example 5

4-(1,3-dioxolan-2-yl)-2,6-dimethoxybenzene boronic acid

1) 4-bromo-3,5-dimethoxybenzaldehyde (3 g) was dissolved in toluene (50 ml) and ethylene glycol (6.8 ml) and catalytic quantity of p-TSA was added. The mixture was refluxed using Dean Stark distillation apparatus overnight, and it was distilled. The residue was refined by silica gel column chromatography (elution liquid, hexane/ethyl acetate 5:1 – 2:1) and 4-bromo-3,5-dimethoxybenzaldehyde ethylene acetal (2.63 g) was obtained.

2). The product obtained as above was treated in the same way as in Production Example 7-(1), and the title compound was thereby obtained.

(0368)

Reference Example 6

2,6-dimethoxy-3-methoxymethoxy benzene boronic acid

1) Acetone (20 ml) solution of 2,4-dimethoxyphenol (3.3 g, J.O.C. 1984, 49, 4740) was added to anhydrous potassium carbonate (3.55 g) dissolved in acetone (10 ml) under nitrogen. Chloromethyl methyl ether (1.79 ml) was added dropwise, and the mixture was stirred at room temperature for 18 hours and thereafter, was heated to 50°C for 24 hours. Additional chloromethyl methyl ether (1.79 ml) was added, and the mixture was stirred at 50°C furthermore for one day, and evaporation was caused. The residue was dissolved in water and extraction was carried out with ethyl acetate. The extraction liquid was dried with magnesium sulfate, filtered, and evaporation was caused. The residue was refined by silica gel column chromatography (elution liquid, hexane/ethyl acetate (20:1 – 10:1)) and 1,3-dimethoxy-4-methoxymethoxy benzene (1.18 g) was obtained.

2). The product obtained as above was treated in the same way as in Production Example 7-(1), except that 1,3-dimethoxybenzene was replaced by the 1,3-dimethoxy-4-methoxymethyloxy benzene, and the title compound was obtained.

(0369)

Reference Example 7

6-methoxy-1,4-benzodioxan-5-yl boronic acid

1) 1,4-benzodioxan-6-carboxy aldehyde (5.20 g) was dissolved in methanol (60 ml) containing concentrated sulfuric acid (0.6 ml). A 30 % hydrogen peroxide water solution (4.7 ml) was added at 0°C over a period of five minutes. The mixture was warmed to room temperature, stirred for 18 hours, and thereafter, it was evaporated. The residue was dissolved in water, and extraction was carried out with methylene chloride. The extract was dried with sodium sulfate, filtered, and evaporation was caused. The residue was refined by silica gel column chromatography (eluate, hexane-hexane / ethyl acetate (3 : 1)) and 6-hydroxy-1,4-benzodioxan (3.85 g) was obtained.
ESMS : m/z 153 MH+.

2) Iodomethane (2.3 ml) was added to DMF (10 ml) liquid mixture of the product obtained as above (3.83 g), potassium carbonate (7.0 g) and n-Bu4NI (186 mg), and it was stirred under nitrogen at room temperature for 24 hours, the mixture was filtered and was washed three times with ethyl acetate (15 ml). The filtrate was washed with aqueous sodium chloride, dried with sodium sulfate, and it was concentrated. The residue was refined by silica gel column chromatography (eluate, hexane-hexane / ethyl acetate (4 : 1)) and 6-methoxy-1,4-benzodioxan (3.25 g) was obtained.
ESMS : m/z 167 (MH+).

3) The product obtained as above was treated in the same way as in Production Example 7-(1), and the title compound was thereby obtained.

(0370)

Reference Example 8

6-methoxy-2-methoxymethoxy benzene boronic acid

The title compound was obtained from 3-methoxyphenol in the same way as in Reference Example 6.

(0371)

Reference Example 9

2,6-dimethoxy-4-[(t-butyl diphenyl silyloxy) methyl] benzene boron acid

1) DMF (60 ml) mixture of 3,5-dimethoxybenzyl alcohol (4.0 g), t-butyl-diphenyl silyl chloride (6.54 g) and imidazole (3.28 g) was stirred at room temperature for 24 hours. The DMF was eliminated by distillation, and the residue was refined by silica gel column chromatography (eluate, hexane - 20 % ethyl acetate solution of hexane) and 3,5-dimethoxy-1-[(t-butyl diphenyl silyloxy) methyl] benzene (8.5 g) was obtained.
ESMS : m/z 407 (MH+).

2) The product obtained as above was treated in the same way as in Production Example 7-(1),

and the title compound was thereby obtained.

ESMS : m/z 451(MH+).

(0372)

Reference Example 10

2,6-dimethoxy-4-(thiomorpholinomethyl) benzene boronic acid

1) Thiomorpholine (3.4 g) was added to 3,5-dimethoxybenzyl chloride (2 g) dissolved in THF (25 ml), and the mixture was stirred at room temperature overnight. Solid material was eliminated by filtration, and the filtrate was evaporated. The residue was refined by silica gel column chromatography (eluate, ethyl acetate / hexane (1 : 2)) and 3,5-dimethoxy-1-(thiomorpholinomethyl) benzene (2 g) was obtained.

ESMS : m/z 253 (M).

2) The product obtained as above was treated in the same way as in Production Example 7-(1), and the title compound was thereby obtained.

(0373)

Reference Example 11

2,6-dimethoxy-4-[(4-t-butoxycarbonyl piperazinyl) methyl] benzene boronic acid

The title compound was obtained in the same way as in Reference Example 10 except that thiomorpholine was replaced by the N-(t-butoxycarbonyl) piperazine.

(0374)

The following compounds (Reference Examples 12-17) were obtained in the same way as in Reference Example 10 except that thiomorpholine was replaced by the necessary amines.

Reference Example 12: 2,6-dimethoxy-4-[(diethylamino) methyl] benzene boronic acid,

Reference Example 13: 2,6-dimethoxy-4-(piperidinomethyl) benzene boronic acid,

Reference Example 14: 2,6-dimethoxy-4-(morpholinomethyl) benzene boronic acid,

Reference Example 15: 2,6-dimethoxy-4-[(4-benzyl-1-piperazinyl) methyl] benzene boronic acid,

Reference Example 16: 2,6-dimethoxy-4-[(dimethylamino) methyl] benzene boronic acid,

Reference Example 17: 2,6-dimethoxy-4-[(4-t-butoxycarbonyl piperazinyl) methyl] benzene boronic acid.

(0375)

Reference Example 18

2,6-dimethoxy-4-(2-hydroxyethyl) benzene boronic acid.

1) (3,5-dimethoxy) phenyl acetic acid (3 g) dissolved in diethyl ether (100 ml) was cooled to 0°C, and 1 M diethyl ether solution (16.8 ml) of LiAlH4 was added. The mixture was warmed to room temperature and was stirred for five hours, and the pH was adjusted to pH 5 using 1 M hydrochloric acid. The mixture was washed with water / ethyl acetate, and the organic layer was separated. The aqueous layer was extracted with ethyl acetate, and the recovered organic layer was dried with magnesium sulfate, and was vacuum concentrated, and 3,5-dimethoxy-4-(2-hydroxyethyl) benzene (2.8 g) was obtained as crude product.

2) The product obtained as above was treated in the same way as in Production Example 7-(1), and the title compound was thereby obtained.

(0376)

Reference Example 19

2,6-dimethoxy-4-(t-butyl diphenyl silyloxy) benzene boronic acid

1) DMF (60 ml) mixture of 3,5-dimethoxyphenol (4.0 g), t-butyl-diphenyl silyl chloride (6.54 g) and imidazole (3.28 g) was stirred at room temperature for 24 hours. The DMF was eliminated by distillation, and the residue was refined by silica gel column chromatography (eluate, hexane - 20 % ethyl acetate solution of hexane) and 3,5-dimethoxyphenyl-t-butyl diphenyl silyl ether (8.5 g) was obtained.

ESMS : m/z 407 (MH+).

2) The product obtained as above was treated in the same way as in Production Example 7, and the title compound was thereby obtained.

ESMS : m/z 451 (MH+).

(0377)

Reference Example 20

2,6-dimethoxy-4-hydroxymethyl benzene boronic acid

3,5-dimethoxybenzyl alcohol was treated in the same way as in Production Example 7, and the title compound was thereby obtained.

(0378)

Reference Example 21

2,6-dimethoxy-3-hydroxymethyl benzene boronic acid

2,4-dimethoxybenzyl alcohol was treated in the same way as in Production Example 7, and the title compound was thereby obtained.

(0379)

Reference Example 22

1-bromo-2,4-dimethoxy-6-cyanobenzene

Pyridinium tri bromide (4 g) was added to methylene chloride (100 ml) solution of 3,5-dimethoxybenzo nitrile (2 g). The mixture was stirred at room temperature for 24 hours, and it was washed successively with sodium bicarbonate aqueous solution, water and aqueous sodium chloride and was dried with magnesium sulfate, filtered, and evaporation was caused. The residue was crystallised from the methylene chloride and hexane, and the title compound (1.8 g) was obtained.

(0380)

Reference Example 23

N-allyl-N-t-butoxycarbonyl-4-bromo-3,5-dimethoxy aniline.

1) 3,5-dimethoxy aniline (7.55 g) was dissolved in methylene chloride (100 ml) under nitrogen, and the solution was cooled to -78°C. Methylene chloride (100 ml) solution of tetrabutyl ammonium tri bromide (25 g) was added, and the mixture was stirred at the same temperature for 45 minutes. The mixture was left to stand to room temperature, and it was warmed and was stirred for one hour 30 minutes and extraction was carried out with 1N hydrochloric acid. The liquid extract was neutralized with 3N sodium hydroxide, and extraction was carried out with ethyl acetate. The liquid extract was dried with magnesium sulfate, filtered, and evaporation was caused. The residue was refined by silica gel column chromatography (eluate, hexane / ethyl acetate (4:1 – 2:3) and 4-bromo-3,5-dimethoxy aniline (3.76 g) was obtained.

2) The product obtained as above(3 g) was dissolved in anhydrous THF (25 ml) under nitrogen, and DIEA (5.4 ml) was added. Anhydrous THF (20 ml) solution of di-t-butyl dicarbonate (3.39 g) was added, and 3.5 day was stirred the mixture by 45°C. the solvent was eliminated by distillation, and the residue was dissolved in ethyl acetate, and it was washed successively with 1N hydrochloric acid, saturated sodium bicarbonate solution and aqueous sodium chloride. The organic layer was dried with magnesium sulfate, filtered, and evaporation was caused. The residue was refined by silica gel column chromatography (eluate, hexane / ethyl acetate (4 : 1)) and a solid was obtained. The obtained solid material was triturated with hexane, and remaining di-t-butyl dicarbonate was eliminated, and N-t-butoxycarbonyl-4-bromo-3,5-dimethoxy aniline (3.67 g) was filtered, and it was isolated.

3) 60 % sodium hydride (0.585 g) was added to anhydrous THF / DMF (100/6 m L) solution of product obtained as above, and the mixture was stirred for several minutes. Allyl bromide (1.13 ml) was added, and the mixture was stirred at room temperature overnight, and it was concentrated, and the residue was refined by silica gel column chromatography (eluate, hexane / ethyl acetate (4 : 1)) and the title compound (3.96 g) was obtained.

(0381)

Synthesis of benzoic acid species

Reference Example 24:

4-amino-2,6-dichloro benzoic acid methyl ester

1) Anhydrous methylene chloride (60 ml) and thionyl chloride (40 ml) were added to 2,6-dichloro-4-nitrobenzoic acid (12.8g, US Patent No. 3423475), and thereafter the obtained mixture was refluxed for 19 hours. The mixture was allowed to cool to room temperature, and evaporation was caused. Additional methylene chloride (10 ml) was added, and thereafter the solution was evaporated. Methanol (100 ml) was added to the residue, and the mixture was refluxed for 17 hours. The mixture was allowed to cool to room temperature, and it could be introduced into ice bath. Precipitated solid material was recovered by filtration, and 2,6-dichloro-4-nitrobenzoic acid methyl (10.8 g, 80 %) was obtained.

2) Water (100 ml) solution of Na2S2O4 (45 g) was added to ethanol (250 ml) solution of product obtained as above. The mixture was refluxed for two hours and was stirred at room temperature overnight, and it was filtered, and it was concentrated. The residue was dissolved in 1N hydrochloric acid (250 ml) and was stirred for two hours, and it was neutralized with 10 % sodium hydroxide and extraction was carried out with ethyl acetate. The liquid extract was dried with magnesium sulfate, filtered, and evaporation was caused. The residue was recrystallised from ethyl acetate / hexane, and the title compound (7.48 g) was obtained.

(0382)

Reference Example 25

4-bromo-2,6-dichloro benzoic acid and 4-bromo-2,6-dichlorobenzoyl chloride

1) 4-amino-2,6-dichloro benzoic acid methyl ester (1.00 g) were suspended in 40 % hydrobromic acid aqueous solution, and the mixture was cooled to 0-5°C. Sodium nitrite (376 mg) was added a little at a time, and the mixture was stirred for about five minutes. Copper (100 mg) was added, and the mixture was warmed to 100°C. The mixture was stirred at 100°C for 30 minutes, and it was diluted with water and extraction was carried out with ethyl acetate. The liquid extract was dried with magnesium sulfate, filtered, and evaporation was caused. The residue was refined by silica gel column chromatography (eluate, hexane / ethyl acetate (50:1)) and 4-bromo-2,6-dichloro benzoic acid methyl ester (1.07 g) was obtained.

2) The product obtained as above (1.06 g) was dissolved in THF / methanol (6 : 1, 50 mL) and 1M lithium hydroxide (7.47 ml) was added. The mixture was refluxed for one day, and evaporation was caused, and the residue was dissolved in water (50 ml) and the pH was adjusted with two or less with 1N hydrochloric acid. The mixture was extracted with ethyl acetate and was

dried with magnesium sulfate, filtered, and evaporation was caused, and 4-bromo-2,6-dichloro benzoic acid (0.94 g) was obtained.

3) Thionyl chloride (2.51 ml) was added to methylene chloride (20 ml) solution of product the obtained as above. The mixture was refluxed for five hours, and evaporation was caused, and it formed into an azeotrope with methylene chloride, and 4-bromo-2,6-dichlorobenzoyl chloride was obtained.

(0383)

Reference Example 26

2,6-dichloro-4-hydroxybenzoic acid

1) 4-amino-2,6-dichloro benzoic acid methyl ester (0.5 g) was suspended in 20 % hydrochloric acid (25 ml) and the mixture was cooled to 0-5°C after stirring for 30 minutes. After addition, mixture was stirred at the same temperature slowly for 30 minutes, and thereafter, sodium nitrite (188 mg) was added to boiling water (50 ml). The mixture was refluxed for two hours and was allowed to cool to room temperature and was dried with extraction, magnesium sulfate with ethyl acetate, and it was filtered, and evaporation was caused. The residue was refined by silica gel preparative TLC (eluate, methylene chloride) and 2,6-dichloro-4-hydroxybenzoic acid methyl ester (275 mg) was obtained.

2) To THF / methanol (6:1, 25 mL) solution of product obtained as above (265 mg), 1M sodium hydroxide (3.6 ml) was added, and the mixture was refluxed for one day. 1N sodium hydroxide (3.6 ml) was added, and the mixture was refluxed furthermore for one day. The mixture was evaporated, and the residue was dissolved in water, and the mixture was adjusted to pH 2 or less with 1N hydrochloric acid, and it was extracted with ethyl acetate containing small amount of methanol. The liquid extract was dried with magnesium sulfate, filtered, and evaporation was caused, and the title compound (248 mg) was obtained.

(0384)

Reference Example 27

2,6-dichloro-4-fluorobenzoic acid

1) 4-amino-2,6-dichloro benzoic acid methyl ester (0.5 g) was suspended in 15 % hydrochloric acid (10 ml) and the mixture was cooled to 0-5°C after stirring for 30 minutes. Sodium nitrite (188 mg) was added a little at a time, and the mixture was stirred at the same temperature for 30 minutes. HBF4 (0.46 ml) which was cooled beforehand was added, and the mixture was stirred for 30 minutes. The obtained precipitate was recovered, and it was washed successively with cold water, methanol and ether. Thereafter, solid material was dried using concentrated sulfuric acid in vacuum desiccator for several days. It was heated till all solids fused a solid with bunsen burner.

The obtained gaseous material was recovered on water (using distillation apparatus). Product was recovered with diethyl ether. the solvent was eliminated by distillation, and crude product was refined by silica gel preparative TLC (eluate, hexane/ ethyl acetate (50:1 – 20:1)) and 2,6-dichloro-4-fluorobenzoic acid methyl ester (241 mg) was obtained.

2) TMSI (164 ml) was added to the product obtained as above (233 mg) dissolved in carbon tetrachloride. The mixture was stirred at 50°C under nitrogen for two days. Water was added, and the mixture was stirred for one hour. 1N hydrochloric acid (25 ml) was added, and the mixture was extracted with ethyl acetate. The liquid extract was dried with magnesium sulfate, filtered, and evaporation was caused. The residue was refined by silica gel column chromatography (eluate, gradient elution of chloroform / methanol) and the title compound 38 mg was obtained.

(0385)

Reference Example 28

2-chloro-4-(2-thiazolinyl amino) benzoic acid

1) THF (20 ml) mixture of 4-amino-2-chlorobenzoic acid methyl ester (0.5 g) and 2-chloroethyl isothiocyanate (0.26 ml) was refluxed for 24 hours. The THF was eliminated by distillation, and the residue was refined by silica gel column chromatography (eluate, hexane) and 2-chloro-4-(2-thiazolinyl amino) benzoic acid methyl ester (74 mg) was obtained.
ESMS : m/z271 (MH+).

2) The product obtained as above was hydrolysed with LiOH, and the title compound (43 mg) was obtained.
ESMS : m/z 257 (MH+).

(0386)

Reference Example 29

2-chloro-4-(2-oxazolinyl amino) benzoic acid

1) THF (20 ml) mixture of 4-amino-2-chlorobenzoic acid methyl ester (0.5 g) and 2-chloroethyl isocyanate (0.23 ml) was heated under reflux for 24 hours. The THF was eliminated by distillation, and the residue was refined by silica gel column chromatography (eluate, hexane / ethyl acetate (3:1 – 1:1)) and 4-[3-(2-chloroethyl) ureide]-2-chlorobenzoic acid methyl ester (0.63 mg) was obtained.
ESMS : m/z 291 (MH+).

2) Sodium methoxide (0.21 g) was added to the product obtained as above (0.58g) dissolved in THF (20 ml), and it was refluxed overnight. The THF was eliminated by distillation, and the residue was extracted with ethyl acetate. The liquid extract was washed with water and was dried

with magnesium sulfate, and evaporation was caused. The residue was refined by silica gel column chromatography (eluate, ethyl acetate) and 2-chloro-4-(2-oxazolidinyl amino) benzoic acid methyl ester (0.46 g) was obtained.
ESMS : m/z 254 (MH+).

3) The product obtained as above was hydrolysed with LiOH, and the title compound was thereby obtained.
ESMS : m/z 240 (MH+).

(0387)

Reference Example 30

2-chloro-4-(2-oxo-1-pyrrolidinyl) benzoic acid

1) To methylene chloride (20 ml) solution of 4-amino-2-chlorobenzoic acid methyl ester hydrochloride (0.52 g) and DIEA (0.27 ml), 4-chloro butyryl chloride (0.3 ml) was added at 0°C under nitrogen, and the mixture was stirred at the same temperature for four hours. DMAP (0.23 mg mole) was added, and the mixture was stirred at room temperature overnight. 4-chloro butyryl chloride (0.3 ml) and DIEA (0.09 ml) were added, and the mixture was stirred for 24 hours. The mixture was diluted with methylene chloride (100 ml), and the solution was washed successively with 1N hydrochloric acid, saturated sodium bicarbonate solution, aqueous sodium chloride, and drying was evaporated. The residue was refined by silica gel column chromatography (eluate, hexane / ethyl acetate (3 : 1)) and 4-(4-chloro butyryl) amino-2-chlorobenzoic acid methyl ester (0.64 g) was obtained.
ESMS : m/z 290(MH+).

2) Sodium methoxide (0.33 g) was added to the product obtained as above (0.64 g) dissolved in THF (20 ml), and it was refluxed for three hours. The THF was eliminated by distillation, and the residue was distributed between ethyl acetate and water. The ethyl acetate layer was separated and recovered, and the aqueous layer was extracted with ethyl acetate. Recovered extract was dried with magnesium sulfate, and evaporation was caused. The residue was refined by silica gel column chromatography (eluate, hexane / ethyl acetate (1 : 1)) and 2-chloro-4-(2-oxo-1-pyrrolidinyl) benzoic acid methyl ester was obtained. ESMS : m/z 254(MH+).

3) The product obtained as above was hydrolysed with LiOH, and the title compound was thereby obtained.
ESMS : m/z 240 (MH+).

(0388)

Reference Example 31

2-chloro-4-(1-pyrrolyl) benzoic acid

1) Acetic acid (16 ml) solution mixture of 4-amino-2-chlorobenzoic acid methyl ester (0.46 g) and 2,5-dimethoxy tetrahydrofuran (0.33 ml) was heated under reflux for two hours. The mixture was cooled to room temperature, and it was diluted with water and extraction was carried out with ethyl acetate. The liquid extract was washed with saturated sodium bicarbonate and aqueous sodium chloride and was dried with magnesium sulfate, filtered, and evaporation was caused. The residue was refined by silica gel column chromatography (eluate, hexane / ethyl acetate (5 : 1)) and 2-chloro-4-(1-pyrrolyl) benzoic acid methyl ester (0.48 g) was obtained.
ESMS : m/z 236(MH+).

2) The product obtained as above was hydrolysed with LiOH, and the title compound was thereby obtained.
ESMS : m/z 220(M-H)-.

(0389)

Reference Example 32

2-chloro-4-(2-trifluoroacetyl-1-pyrrolyl) benzoic acid

1) Anhydrous trifluoroacetic acid (0.55 ml) was added to methylene chloride (5 ml) solution of 2-chloro-4-(1-pyrrolyl) benzoic acid methyl ester (0.3 g) and stirred at room temperature for four hours. The mixture was diluted with methylene chloride and the mixture was stirred together with saturated sodium bicarbonate solution for 30 minutes. The organic layer was separated and was washed in aqueous sodium chloride and was dried with magnesium sulfate, filtered, and evaporation was caused. The residue was refined by silica gel column chromatography (eluate, hexane / ethyl acetate (5 : 1)) and 2-chloro-4-(2-trifluoroacetyl-1-pyrrolyl) benzoic acid methyl ester (0.4 g) was obtained.
ESMS : m/z 330 (M-1).

2) The product obtained as above was hydrolysed with LiOH, and the title compound was thereby obtained.
ESMS : m/z 318 (MH+).

(0390)

Reference Example 33

2-chloro-4-(2,5-dichloro-1-pyrrolyl) benzoic acid

1) N-chlorosuccinimide (0.56 g) was added to ice cooled THF (7 ml) solution of 2-chloro-4-(1-pyrrolyl) benzoic acid methyl ester (0.5 g) under nitrogen. The mixture was warmed to room temperature and was stirred overnight. THF was eliminated, and the residue was treated with diethyl ether, and it was filtered. The filtrate was eliminated by distillation, and the residue was

refined by silica gel column chromatography (eluate, hexane / ethyl acetate (10:1)) and 2-chloro-4-(2,5-dichloro-1-pyrrolyl) benzoic acid methyl ester (0.61 g) was obtained.
ESMS : m/z 306 (MH+).

2) The product obtained as above was hydrolysed with LiOH, and the title compound was thereby obtained.
ESMS : m/z 290 (MH+).

(0391)

Reference Example 34

2-chloro-4-(2-formyl-1-pyrrolyl) benzoic acid

1) Methylene chloride (2 ml) solution of DMF (0.1 ml) was added dropwise with stirring at –30°C under nitrogen to methylene chloride (16 ml) solution of oxalyl chloride (0.2 ml). The mixture was stirred for 15 minutes, and 2-chloro-4-(1-pyrrolyl) benzoic acid methyl ester (0.5 g) dissolved in DMF (4 ml) was added. The mixture was stirred at the same temperature for three hours, and it was left to stand to room temperature, and it was warmed. The mixture was stirred overnight, and evaporation was caused. The residue was caused to undergo liquid separation with ethyl acetate and 0.2M sodium acetate. The ethyl acetate layer was separated, and the aqueous layer was extracted with ethyl acetate. The recovered ethyl acetate layer was washed in aqueous sodium chloride and was dried with magnesium sulfate, filtered, and evaporation was caused. The residue was refined by silica gel column chromatography (eluate, hexane / ethyl acetate (3 : 1)) and 2-chloro-4-(2-formyl-1-pyrrolyl) benzoic acid methyl ester (0.41 g) was obtained.
ESMS : m/z264(MH+).

2) The product obtained as above was hydrolysed with LiOH, and the title compound was thereby obtained.
ESMS : m/z 248(M-H)-.

(0392)

Reference Example 35

2-chloro-4-[N-methyl-N-(methylsulfonyl) amino] benzoic acid

1) A dioxane (15 ml) solution of di-t-butyl dicarbonate (1.39 g) was added dropwise to ice cooled 1N sodium hydroxide (12.8 ml) solution of 4-amino-2-chlorobenzoic acid (1.0 g). The mixture was left to stand to room temperature, and it was warmed and was stirred overnight. Dioxane was eliminated, and aqueous solution was extracted with diethyl ether. The aqueous solution was made acidic to less than pH2 with 1N hydrochloric acid. Precipitated solid material was recovered by filtration and was washed with 1N hydrochloric acid and water, and it was dried under vacuum, and 4-(t-butoxycarbonyl amino)-2-chlorobenzoic acid (1.13 g) was obtained.

ESMS : m/z 294 (MH+).

2) Sodium methoxide (0.16 g) was added to the product obtained as above (0.36 g) dissolved in DMF (10 ml) under nitrogen. The mixture was cooled to 0°C, and iodomethane (0.5 ml) was added. The mixture was stirred at room temperature overnight. Sodium methoxide (0.14 g) and iodomethane (0.55 ml) were added, and also it was stirred for six hours. THF was eliminated, and the residue was distributed to ethyl acetate and water. The ethyl acetate layer was separated, and the aqueous layer was extracted with ethyl acetate. The recovered ethyl acetate layer was washed with aqueous sodium chloride and was dried with magnesium sulfate, filtered, and evaporation was caused. The residue was refined by silica gel column chromatography (eluate, hexane / ethyl acetate (1 : 1)) and 2-chloro-4-[N-methyl-N-(t-butoxycarbonyl) amino] benzoic acid methyl ester (0.38 g) was obtained.
ESMS : m/z322 $(M+Na)^+$.

3) Methylene chloride (10 ml) solution of the product obtained as above was treated with TFA (5 ml) for two hours. The mixture was evaporated, and the residue was dissolved in ethyl acetate. The ethyl acetate solution was washed successively with 10 % sodium carbonate and aqueous sodium chloride and was dried with magnesium sulfate, filtered, and 2-chloro-4-(methylamino) benzoic acid methyl ester (0.25 g) was obtained.
ESMS : m/z 200(MH+).

4) Methanesulfonyl chloride (0.2 ml) was added to methylene chloride (20 ml) solution of the product obtained as above (0.25g) and pyridine (0.2 ml) under nitrogen and was heated at 40°C for 4 hours. Pyridine (0.2 ml) and methanesulfonyl chloride (0.2 ml) were added, and liquid mixture was heated for two hours. The mixed liquid was diluted with methylene chloride and was washed with 1 N hydrochloric acid and water and was dried with magnesium sulfate, filtered, and evaporation was caused. The residue was refined by silica gel column chromatography (eluate, hexane / ethyl acetate (3:1 – 1:1)) and 2-chloro-4-[N-methyl-N-(methanesulphonyl) amino] benzoic acid methyl ester (0.26 g) was obtained.
ESMS : m/z 278(MH+).

5) The product obtained as above was hydrolysed with LiOH, and the title compound was thereby obtained.
ESMS : m/z 264(MH+).

(0393)

Reference Example 36

2-chloro-4-thiouredide benzoic acid

1) Benzoyl chloride (0.31 ml) and ammonium thiocyanate (0.20 g) dissolved in acetone (15 ml) were refluxed for 30 minutes, and benzoyl thiocyanate was generated. 4-amino-2-chlorobenzoic acid methyl ester (0.5g)dissolved in acetonitrile (10 ml) was added to this solution, and it was refluxed for five hours. The solvent was eliminated, and the residue was distributed to methylene chloride and water. The organic layer was separated and recovered and was washed with aqueous sodium chloride and was dried, and evaporation was caused. The residue was refined by column chromatography, and 2-chloro-4-(3-benzoyl thiouredide) benzoic acid methyl ester (0.71 g) was obtained.
ESMS : m/z349(MH+).

2) The product obtained as above was hydrolysed with LiOH, and the title compound was thereby obtained.
ESMS : m/z 231(MH+).

(0394)

Reference Example 37

2,6-dichloro-4-phenylbenzoic acid

1) Benzene boron acid (1.30 g), Pd(PPh3)4 (0.16g) and 2 M sodium carbonate (5 ml) were added to 2,6-dichloro-4-bromobenzoic acid methyl ester (0.55g) dissolved in THF (10 ml). The mixture was refluxed under nitrogen for four hours. After cooling, mixture was diluted with ethyl acetate and was washed with water and aqueous sodium chloride. The organic layer was dried with sodium sulfate, and it was filtered, and it was concentrated. The residue was refined by silica gel preparative TLC (eluate, hexane-ethyl acetate / hexane (1 : 1)) and 2,6-dichloro-4-phenylbenzoic acid methyl ester (0.57 g) was obtained.
ESMS : m/z 281 (MH+).

2) The product obtained as above was hydrolysed with LiOH, and the title compound was thereby obtained.
ESMS : m/z 267(MH+), 265(M-H)-.

(0395)

Reference Example 38

2,6-dichloro-4-[2-(N-methyl) pyrrolyl] benzoic acid (J. Med, Chem, 41, 2019 (1998)).

1) 2,6-dichloro-4-[2-(N-t-butoxycarbonyl) pyrrolyl] benzoic acid methyl ester was obtained in the same way as in Reference Example 37-1) except that 2-(N-t-butoxycarbonyl) pyrrole boronic acid was used instead of benzene boronic acid.

2) TFA (5 ml) was added to methylene chloride (5 ml) solution of product obtained as above.

After 2 hours under nitrogen, mixture was diluted with methylene chloride and was washed with water and aqueous sodium chloride and was dried with sodium sulfate, and it was filtered, and it was concentrated, and 2,6-dichloro-4-(2-pyrrolyl) benzoic acid methyl ester was obtained.

3) Sodium hydride (0.07 g) and iodomethane (0.14 ml) were added to the product obtained as above (0.20 g) dissolved in THF (5 ml). It was stirred at room temperature for two hours and thereafter, mixture was diluted with ethyl acetate and was washed with water and aqueous sodium chloride. The organic layer was dried with sodium sulfate, and it was filtered, and it was concentrated. The residue was refined by TLC for silica gel fractionation (eluate, ethyl acetate / hexane (1:10)), and 2,6-dichloro-4-[2-(N-methyl) pyrrolyl] benzoic acid methyl ester (0.088 g) was obtained.

4) The product obtained as above was hydrolysed with LiOH, and the title compound was thereby obtained.

(0396)

Reference Example 39

3-bromo-2,6-dichloro benzoic acid

1) Methylene chloride (30 ml) solution of tetrabutyl ammonium tribromide (6.94 g) was added dropwise at 10°C by 10°C to methylene chloride (20 ml) solution of 2,6-dichloro-4-aminobenzoic acid methyl ester (2.80 g). Two hours were allowed to pass, and the mixture was warmed to room temperature and was washed with saturated sodium bicarbonate liquid and aqueous sodium chloride and was dried with sodium sulfate, and it was filtered, and it was concentrated. The residue was refined by silica gel column chromatography (eluate, ethyl acetate /hexane (1 : 4)) and 2,6-dichloro-3-bromo-4-aminobenzoic acid methyl ester (2.99 g) was obtained.
ESMS : m/z 298 (MH+).

2) Sodium nitrite (0.73 g) was added to sulphuric acid (10 ml) and water (20 ml) solution of 0°C of product obtained as above(2.99g). After 15 minutes, the mixture was treated with H3PO2. After 60 minute, the mixture was extracted with ethyl acetate. The liquid extract was washed with saturated sodium bicarbonate and aqueous sodium chloride and was dried with sodium sulfate, and it was filtered, and it was concentrated. The residue was refined by silica gel column chromatography (eluate, hexane - ethyl acetate / hexane (1:10)) and 2,6-dichloro-3-bromobenzoic acid methyl ester (2.11 g) was obtained.
ESMS : m/z 282(MH+).

3) The product obtained as above was hydrolysed with LiOH, and the title compound was thereby obtained.

ESMS: m/z 268 (MH+) and 266 (M^--1).

(0397)

Reference Example 40

2-chloro-4-(t-butoxycarbonyl) benzoic acid

1) 3-chloro-4-methoxycarbonyl benzoic acid (0.24 g) was dissolved under nitrogen in DMF (2.5 ml), and thereafter, CDI (0.36 g) was added, and the obtained mixture was stirred at 40°C for two hours. t-butanol (0.54 ml) and DBU (0.33 ml) were added, and it was stirred at 40°C for two days. The mixture was evaporated, and the residue was dissolved in ethyl acetate and was washed with 1 N hydrochloric acid and saturated sodium bicarbonate liquid and was dried with magnesium sulfate, filtered, and evaporation was caused. The residue was refined by silica gel column chromatography (eluate, toluene) and 2-chloro-4-(t-butoxycarbonyl) benzoic acid methyl ester (216 mg) was obtained.

2) The product obtained as above was hydrolysed with LiOH, and the title compound was thereby obtained.

(0398)

Reference Example 41

4-(N,N-dimethyl sulphamoyl) amino-2-chlorobenzoic acid

1) pyridine (0.4 ml) was added to methylene chloride (10 ml) solution of 4-amino-2-chlorobenzoic acid methyl (0.3 g) under nitrogen by 0°C. N,N-dimethyl sulfamoyl chloride (0.21 ml) was added, and the mixture was stirred at room temperature for 16 hours, and it was refluxed for five hours. DMAP (0.4 g) was added, and the mixture was stirred for three hours. The mixture was diluted with methylene chloride 100 mL, and it was washed successively with 1N hydrochloric acid, aqueous sodium chloride, saturated sodium bicarbonate solution and aqueous sodium chloride, and drying and evaporation were carried out. The residue was refined by silica gel flash column chromatography (eluate, ethyl acetate /hexane (1 : 3)) and 4-(N, N-dimethyl sulphamoyl) amino-2-chlorobenzoic acid methyl (0.31 g) was obtained.
ESMS : m/z 293 (MH+).

2) The product obtained as above was hydrolysed with LiOH in the same way as in Production Example 1-5), and the title compound was thereby obtained.
ESMS : m/z 279(MH+).

(0399)

Reference Example 42

Trimethyl-(2-cyano-3-thienyl) tin

Toluene (8 ml) mixture of 3-bromothiophene-2-carbonitrile (385 mg), hexamethyl 2 tin (615 mg) and Pd(PPh3)4(116mg) were stirred at 130°C under nitrogen for 16 hours. The organic layer was eliminated by distillation under reduced pressure, and the residue was refined by silica gel column chromatography (eluate, ethyl acetate / hexane (1:3)) and the title compound (406 mg) was obtained.

(0400)

Reference Example 43

2,6-di (methoxymethoxy) benzene boronic acid

1) DIEA (26 ml) and methoxymethoxy chloride (8.20 ml) were added to methylene chloride (40 ml) suspension of 3.65 g resorcin at 0°C under nitrogen. The mixture was stirred at the same temperature for ten minutes, and it was stirred at room temperature for 16 hours. DIEA (13 ml) and methoxymethoxy chloride (4 ml) were added to mixture, and it was stirred for one hour. The mixture was added to water, and extraction with chloroform was carried out. The liquid extract was dried with magnesium sulfate, and evaporation was caused, and the residue was refined by silica gel flash column chromatography (eluate, 15 % hexane solution of ethyl acetate) and 1,3-di (methoxymethoxy) benzene (2.44 g) was obtained.

2) The product obtained as above was treated in the same way as in Production Example 7-1), and the title compound was thereby obtained.

(0401)

RPM1-CS-1 cell adhesion test.

The following test proved the action of the compounds of this invention in α 4 interstitial cell adhesion inhibition, which is a typical in vitro system. In this test, the adhesion interaction of B cell system RPM1 which is known to express α4 β7 to another spliced region of fibronectin known as CS-1 is measured in the presence of the compounds of this invention (Eel et al. J. Immunol. 153: 517-528 (1994)). The test compound was added with increased concentrations to RPM1 cells, and thereafter, cells-compound mixture was added to CS-1 coated micro well. It was incubated, and plate was washed, and proportion of bonded cells were determined. This test shows directly proves the cell adhesion inhibiting activity and the adhesion regulation activity of the compounds of this invention.

(0402)

RPM1-CS-1 test.

CS-1 derived peptide, CLHPGEILDVPST and control peptide with changed sequence, CLHGPIELVSDPT were synthesized with Beckman 990 synthesizer using t-Boc system. 3-(2-pyridyldithio) propionic acid N-hydroxysuccinimido ester (SPDP) was used as heterologous

divalent crosslinking agent, and the peptide was immobilised on microplate (Pierschubacher et al. Proc, Natl, Acad, Sci, USA, 80: 1224-1227 (1983)). Microplate was film-coated at room temperature with 20 μg/mL human serum albumin (HSA) for two hours, and it was washed once with PBS, and it was derivitised with 10 μg/mL SPDP for one hour. After washing, 100 μg/mL cysteine containing peptide liquid 100 μl which was freshly dissolved was added to each well, and crosslinked on the plate at 4°C overnight. Unbound peptide was washed with PBS, and it was removed from the plate. In order to block unreacted site, the plate was film-coated with 2.5mg/mL PBS solution 100 μl of BSA for one hour at 37°C. Ovary albumin added Dulbecco modified Eagle culture medium (DMEM) solution (2.5×10^6 cells/mL) 100 μl of 0.25 % RPM1 cells was added to peptide coated plate and this was incubated at 37°C for one hour. After this incubation, the plate was washed three times using EL404 plate washer with PBS and the number of adhered cells was determined by measuring enzyme activity of intrinsic N-acetyl-hexosaminidase (Landegren, J, Immunol, Methods. 67: 379-388 (1984)). Therefore, enzyme substrate p-nitrophenyl-N-acetyl-β-D-glucose aminide was dissolved with concentration of 7.5 mM in 0.1M citric acid buffer pH5, and it was mixed with equivalent amount of 0.5 % Triton X100. The substrate solution 50 μl was added to the plate, and the plate was incubated at 37°C for 60 minutes. 50 mM glycine (100 ml), 5mM EDTA buffer pH10.4 was added, and the reaction was stopped. The quantity of freed p-nitrophenol was measured by reading optical density at 405 nm by vertical pathway spectrophotometer equipped with measurement device (VMAX kinetic microplate reader, MOLECULAR DEVICES, Menlo Park, California). This process is a modified process of a previously disclosed process (Caldalli et al, J. Biol. Chem. 269 : 18668-18673 (1994)). In this test, the IC50 value range (mM) is represented by A, B, C and D. These range is as follows.

$D > 5 \geq C > 1 \geq B > 0.3 \geq A$

The following Tables 33-48 show the IC50 values in RPM1-CS-1 test of the selected compounds of this invention. The range is as described above.

(0403)

Table 33

Production Ex. No.

	RPMI-CS-1
1A	B
1B	A
2	C
3	A
4A	C
4B	B
5	C
6	D
7A	A
7B	A
8	A
9	A
10	A
11	A
12	A
13	A
14	A
15	B
16	A
17	A
18	D

(0404)

Table 34

19	C
20	A
21	A
22	C
23	B
24	A
25	B
26	B
27	A
28	B
29	C
30	B
31	A
32	A
33	B
34	C
35	C
36	A
37	B
38	B
39	B
40	B

(0405)

Table 35

41	C
42	B
43	C
44	B
45	A
46	A
47	A
48	C
49	B
50	A
51	B
52	D
53	C
54	B
55	C
56	B
57	C
58	B
59	C
60	B
61	D
62	A

(0406)

Table 36

63	B
64	A
65	A
66	A
67	B
68	A
69	A
70	A
71	A
72	B
73	A
74	B
75	A
76	D
77	A
78	B
79	A
80	A
81	D
82	D
83	B
84	C

(0407)

Table 37

85	B
86	A
87	B
88	C
89	B
90	B
91	C
92	C
93	D
94	C
95	C
96	B
97	B
100	C
101	D
102	D
103	D
104	D
105	D
106	C
107	C
108	C

(0408)

Table 38

109	D
110	D
111	C
112	B
113	A
114	B
115	C
116	C
117	C
118	C
119	D
120	D
121	C
122	C
123	C
124	C
125	C
126	C
127	D
128	B
129	C
130	D

(0409)

Table 39

131	A
132	A
133	A
134	A
135	A
136	B
137	B
138	A
139	A
140	B
141	B
142	A
143	A
144	A
145	C
146	B
147	A
148	A
149	A
150	A
151	A
152A	A

[0410]

Table 40

152B	A
152C	B
153A	A
153B	A
154	A
155	A
156	A
157	A
158	A
159	A
160	A
161	A
162	A
163	A
164	A
165	A
166	A
167	A
168	A
169	A
170	A
171	A

[0411]

(0411)

Table 41

172	A
173	A
174	A
175	A
176	B
177	A
178	A
179	A
180	A
181	B
182	A
183	A
184	A
186	B
187	A
188	A
189	A
190	A
191	A
192	A
193	A
194	C

(0412)

Table 42

195	B
196	A
197	B
198	A
199	A
200	A
201	A
202	A
203	A
204	A
205	A
206	A
207	A
208	A
209	A
210	C
211	A
212	C
213	C
214	B
215	B
216	C

(0413)

Table 43

217	C
218	C
219	B
220	A
221	C
222	A
223	A
224	C
225	C
226	A
227	A
228	A
229	A
230	B
231	A
232	A
233	B
234	A
235	A
236	A
237	A
238	A

(0414)

Table 44

239	A
240	A
241	A
242	A
243	A
244	A
245	A
246	A
247	A
248	A
250	A
251	A
252	A
253	A
254	A
255	A
256	A
257	A
258	A
259	A
262	A
263A	A

(0415)

Table 45

263B	A
264	A
265	A
266	A
267	D
268	C
269	D
270	A
271	A
272	B
273	C
274	C
275	D
276	D
277	A
278	A
279	A
280	A
281	C
282	C
283	C
284	C

(0416)

Table 46

285	A
286	A
287	B
288	C
289	B
290	C
291	C
292	C
293	C
294	C
295	C
296	A
297	A
298	A
299	A
300	B
301	A
302	A
303	A
304	A
305	B
306	A

(0417)

Table 47

307	A
308	A
309	A
310	A
311	A
312	A
316	A
317	A
319	A
320	A
321	A
322	A
323	A
324	A
325	A
326	A
327	A
328	A
329	C
331	A
332	B
333	A

[0418]

(0418)

Table 48

334	A
335	B
336	A
337	A
338	A
339	A
340	A
341	A
342	A
343	C
344	C
345	B
346	A
347	A
348	A
349	A
350	A
351	A
352	B
353	A
354	A
355	A
356	A

(0419)

Advantages Afforded by this Invention

Medicinal composition of this invention is useful in therapy of diseases accompanied by α4 mediated cell adhesion, for example asthma, diabetes mellitus, rheumatism arthritis, inflammatory enteric disease and gastrointestinal tract and other diseases or the like in which leukocyte invasion of other epithelial tissue (for example skin, urethra, bronchus, articulation synovial membrane) participates.

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